Governing Medical Research

Balancing ethical and scientific values in regulation

Jacqueline van Oijen

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Balanceren van ethische en wetenschappelijke waarden in regelgeving en toezicht

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Voor mijn lieve ouders Coby en Henk† en mijn allerliefste zoon C-J

Table of Contents

Chapter 1

General Introduction

What is the problem?

This thesis focuses on the governance of medical research[1] in the Netherlands. It is an intriguing topic because it encompasses quality assurance in research involving human participants and thus foregrounds the inherent challenge of weighing protection of research participants against the need for reliable research outcomes with a societal impact. In other words, it is about maintaining an equilibrium between the interests of research participants and the interests of society. These two pivotal values, namely safeguarding participants and upholding research integrity, form the bedrock of all the laws, regulations, and standards that govern medical research.

While the significance of these key values is beyond dispute, in practice they are not always immediately apparent, as they are often encapsulated within rules and regulations. Nevertheless, they inherently harbour tensions that demand continuous attention, especially when new developments or dynamics arise. In this thesis, I adopt a governance perspective to explore what is required to ensure that these key values are in proper equilibrium. Specifically, my focus is on the often imperceptible work performed by various actors to promote and safeguard these values and to balance them when they collide.

[1] The Dutch Medical Research Involving Human Subjects Act (WMO) does not explicitly define the term 'medical scientific research'. In order to provide clarity in the field, the Central Committee on Research Involving Human Subjects (CCMO) has introduced a definition in their guideline titled *Definition of medical scientific research* in 2005. According to this definition, 'Medical scientific research refers to investigations addressing questions related to realm of illness and health, including aspects such as aetiology, pathogenesis, signs/symptoms, diagnosis, prevention, outcome or treatment. Such investigations involve the systematic collecting and analysis of data, the objective being to contribute to medical knowledge that has applicability beyond the immediate research participants'. The realm of medical scientific research encompasses clinical trials involving medicinal products. For this type of research, the terms 'clinical trials' or 'clinical trials with medicinal products' are employed. Clinical trials are studies that focus primarily on assessing the efficacy and side effects (safety) of new drugs or other medical interventions (Grit & Van Oijen, 2015). In addition, investigator-initiated trials refer to medical research instigated by individual physician-researchers, aimed at deepening the understanding of diseases and enhancing healthcare practices (Grit & Van Oijen, 2015). For the purpose of my PhD, I employ the overarching term 'medical research' to encompass all aforementioned forms of research.

The development of specific values and ethical guidelines for medical research has its roots in the atrocious medical procedures that thousands of prisoners of war were subjected to during the Second World War. As a response to these revelations, the World Medical Association established the Declaration of Helsinki in 1964, which defines the ethical principles that govern experiments involving research participants. Key aspects are that they should not be exposed to unnecessary risks and that they must furnish their informed consent when participating in research.

Scientific values revolve around the conduct of sound research by principled researchers, resulting in the development of treatments or medications that enhance the health and quality of life of the population. The idea is that these values promote well-founded research that contributes to advancements in medical science. These values also apply for research publications that could lead to career building where additional safeguards are needed to address potential conflicts of interest (Beauchamp & Childress, 2013). Finally, they are applicable for researchers who collaborate to pool expertise and generate the best possible options for carrying out high-impact research.

Over time, the components thought to fall under ethical and scientific values have increased in number. Ethical frameworks and principles that determine whether research is sound and acceptable cover multiple aspects of research, with the protection of research participants viewed as an overarching principle. Other ethical principles are more focused on specific components of research (Timmers et al., 2023). Table 1 provides an overview of ten essential prerequisites for ethical research involving human participants according to Resnik (2008), which largely correspond to the seven principles outlined by Emanuel et al. (2000) that pertain to clinical research studies.

These requirements have served as a basis for defining the two key values:

- Ethical value: safeguarding research participants;
- Scientific value: monitoring safety, ensuring data integrity, and producing reliable and accurate results with anticipated societal benefits.

However, this list has its limitations as it does not fully capture the inherent tensions between different values or requirements.

Table 1 Overview of ethical requirements for research with participants

Ten requirements of ethical research (Resnik, 2008, p. 28)	Description	Seven requirements for evaluating ethics of clinical research studies (Emanuel et al., 2000)	Description
1. Scientific validity	Research should be well-designed and executed; the use of research participants must be necessary to answer scientific questions	Scientific validity	Research must be methodologically rigorous
2. Social value	Research should be expected to produce benefits for society	Value	Enhancements of health or knowledge must be derived from the research
3. Risk minimization	Risks to research participants should be minimized		
4. Benefit/risk justification	The expected benefits of the study to the subjects or society must outweigh the potential risks to the subjects	Favorable risk-benefit ratio	Within the context of standard clinical practice and the research protocol, risks must be minimized, potential benefits enhanced, and the potential benefits to individuals and knowledge gained for society must outweigh the risks
5. Informed consent	Research subjects (or their representatives) should give their informed consent to participate in research	Informed consent	Individuals should be informed about the research and provide their voluntary consent
6. Protection of confidentiality and privacy	The confidentiality and privacy of subjects should be protected to the extent allowable by law	Respect for enrolled subjects	Subjects should have their privacy protected, the opportunity to withdraw, and their well-being monitored
7. Equitable subject selection	The selection of subjects must be equitable; there must be a sound scientific or moral justification for including subjects in research or excluding them from research	Fair subject selection	Scientific objectives, not vulnerability or privilege, and the potential for and distribution of risks and benefits, should determine communities selected as study sites and the inclusion criteria for individual subjects

Table 1 Continued - Overview of ethical requirements for research with participants

Ten requirements of ethical research (Resnik, 2008, p. 28)	Description	Seven requirements for evaluating ethics of clinical research studies (Emanuel et al., 2000)	Description
8. Protection of vulnerable subjects	Vulnerable subjects, such as children, prisoners, or mentally disabled adults, should be protected from harm or exploitation in research		
9. Data and safety monitoring	Research should be monitored to protect subjects from harm and ensure the integrity of the data		
10. Independent review	An independent committee, such as an institutional review board (IRB), should review and oversee research	Independent review	Unaffiliated individuals must review the research and approve, amend, or terminate it

While it may seem that these key values are beyond dispute, ensuring them is anything but straightforward due to the inherent tensions and dynamics. For instance, the introduction of new EU legislation, methodologies, or collaborative practices in the research domain may raise new questions about protecting research participants or ensuring scientific integrity, requiring various actors to take action to safeguard these key values. In this thesis, I employ the concept of institutional work, which encompasses the activities undertaken by actors to create, maintain or disrupt institutional structures (Lawrence & Suddaby, 2006). By adopting a governance lens, which focuses on how these values are promoted and safeguarded, I illuminate how actors interact, engage in institutional work and utilize mechanisms to navigate the challenges presented in an ever-changing landscape across various governance practices while upholding key ethical and scientific values within medical research. The primary aim of this thesis is to understand this institutional work. I expand on this in the following sections, and utilize a illustrative case to clarify how the governance of medical research operates in the Netherlands.

Illustrative case on medical research governance in the Netherlands

Medical research in the Netherlands is regulated through the Medical Research Involving Human Subjects Act (WMO),[2] which has been in effect since 1999. This act incorporates a variety of quality assurance standards aimed at upholding the two key values: protecting research participants against the risks and burdens of medical research without unnecessarily hindering the progress of medical science[3] (Stukart 2012, p. 15). Furthermore, the act assigns relevant actors several responsibilities. Researchers need to obtain informed consent from a research participant (WMO, Article 6) and approval from an accredited Medical Research Ethics Committee (MREC) or Central Committee on Research Involving Human Subjects (CCMO) for their

[2] Staatsblad van het Koninkrijk der Nederlanden. (1998, 161). Wet van 26 februari 1998, houdende regelen inzake medisch-wetenschappelijk onderzoek met mensen (Wet medisch-wetenschappelijk onderzoek met mensen) [Medical Research involving Human Subjects].
[3] Tweede Kamer der Staten-Generaal. (1992). Regelen inzake medische experimenten (Wet inzake medische experimenten). Memorie van toelichting. Vergaderjaar (1911-1992), kamerstuk 22 588 nr. 3 p. 2.

study. This approval process is necessary because it is impossible to allow for every potential circumstance within a single law, necessitating a tailored review for each research project. MRECs conduct an integrated review procedure, during which they carefully consider the key ethical and scientific values of the proposed research. They perform an overall evaluation of how these two key values are safeguarded in the research protocol and monitor the ongoing research. MRECs form an integral part of the Netherlands' decentralized system of public supervision.

The dual objective of the WMO referred to above, which is also reflected in various international regulatory frameworks, entails that medical research involving human participants is permitted under strict conditions. Sponsors of medical research therefore have a specific responsibility to protect research participants. Whether this is investigator-initiated research conducted in hospitals or research sponsored by the pharmaceutical industry, the same rules apply despite the unequal situation (Timmers et al., 2023), specifically that the pharmaceutical industry has a range of experts and financial resources at its disposal to ensure compliance with legal requirements, whereas these resources are less available for investigator-initiated research (Tyndall, 2018).

Navigating through various levels of legislation, diverse contexts and a multitude of stakeholders, the governance of medical research requires the alignment of rules with real-world practices. To explore the concept of governance across these levels and to illustrate the work required to ensure key values in medical research, the following illustrative case examines the responsibilities of a science coordinator at a Dutch teaching hospital. This case sheds light on her roles in advising, coordinating, facilitating and supervising medical research activities.

Illustrative case part I

Over the past two years, the science coordinator, a staff member at a teaching hospital (the result of a merger) has made extensive efforts to establish a research registration system. The aim of registration is to provide an overview of potential risks associated with ongoing research within the hospital, as part of the development of a monitoring system. Until recently, approvals granted

by various MRECs were not shared within the hospital because researchers apply to diverse MRECs. The science coordinator proactively built relationships of trust with these distinct MRECs, culminating in her obtaining access to all approved protocols from each one (cc'd on emails). The creation of a database cataloguing approved research protocols was a huge task resulting in an overview of all ongoing research within the hospital. The science coordinator can also contact the researchers and explain the support they can expect from the scientific office, such as theme-based information lunches for researchers and participation in the monitoring programme.

The establishment of a monitoring system is mandated by the national Association of Top Clinical Teaching Hospitals (STZ). The new Board of Directors of the hospital supported the science coordinator's monitoring plan. A risk-based monitoring system, designed to identify, assess, monitor and mitigate risks of ongoing medical research subject to the Dutch WMO, was created from scratch. The science coordinator learned that a monitoring system can only be implemented when the Board of Directors takes final responsibility for medical research within their organization. This responsibility encompasses decision-making concerning time allocation, costs and fees.

Clinical trials involving medicinal products initiated by pharmaceutical companies, and conducted within this hospital, are consistently monitored by the companies themselves, and therefore not included in the hospital's monitoring plan. For all other medical research subject to the WMO, the hospital's Board of Directors mandated that each research department must appoint a monitor. This necessitated the creation and development of a pool of monitors, a challenging process that required intervention by the Board of Directors when monitors were not appointed. Additionally, departments and researchers required comprehensive information on the implications of ongoing monitoring, with one objective being to promote best research practices among researchers. Research activities include obtaining MREC approval for research protocols and informed consent procedures, training researchers in international Good Clinical Practice (GCP) standards, adapting to new legislation such as the European Union Clinical Trials Regulation

(CTR), which replaced the longstanding European Union Clinical Trials Directive (CTD), managing paperwork – both physical and digital – including delegation logs, and ensuring meticulous data collection.

Progress was incremental and implementing these essential changes demanded considerable persistence: the science coordinator's daily tasks included providing information, garnering support, and addressing challenges as they arose.

This illustrative case reveals how the science coordinator played a crucial role and made substantial efforts to establish an effective research registration system, a fundamental responsibility for an organization engaged in research activities. Furthermore, it highlights the absence of automatic communication between different stakeholders operating at separate governance levels, for example between the hospital and the multiple accredited MRECs. The science coordinator navigated this gap and took responsibility by utilizing available resources to obtain crucial information. To achieve progress, she needed to establish separate communication channels with the MRECs.

Other substantial work that the science coordinator had to undertake was to establish a robust, risk-based monitoring system, a task achievable only thanks to the unwavering support of the Board of Directors. Such support became imperative after an incident at a university medical centre (UMC) in 2008, when the mortality rate was found to be higher among patients administered a new treatment than among those administered a placebo (the Propatria study). A comprehensive review conducted by various supervisory bodies, including the CCMO and the Health and Youth Care Inspectorate (IGJ), highlighted the fact that, according to legal mandates, the Boards of Directors must assume the role of sponsor for investigator-initiated trials (IGJ et al., 2009). A sponsor is responsible for seeing that monitoring is conducted by qualified monitors to ensure compliance with legal requirements, codes of conduct, and the protocol.

Below, I continue with the illustrative case by examining the strategies employed by the science coordinator in response to findings resulting from an IGJ inspection.

Illustrative case part II

The hospital's research policies and practices were inspected by the IGJ. Following weeks of preparation, the hospital's board gathered in the boardroom awaiting the arrival of the Inspectorate. In the preceding weeks, the science coordinator had meticulously crafted a self-assessment report and diligently rehearsed for the inspection visit. Refreshments (cookies and coffee) were arranged, and many elements contributed to a well-prepared environment.

During the inspection, the Inspectorate posed questions to the Board of Directors, the secretary of the science committee, and the science coordinator about procedures for monitoring and archiving, the storage of research materials, and communication with researchers.

The Inspectorate had previously communicated which department it would be visiting, and at the start of the day they disclosed which investigator-initiated study had been selected for inspection: a multicentre investigator-initiated study. The science coordinator had asked to attend the meeting between the researchers and the IGJ as an observer, a decision that yielded significant insights. Notably, it was evident that the questions put to these researchers were fundamentally similar, but that their responses differed significantly. One crucial question revolved around the data management of research materials – how and where they should be archived. The studies in which the researchers were involved were part of a collective effort within the region that had a particularly strong affiliation with one of the UMCs. To the dismay of the science coordinator, it became clear that her hospital's informed consent documents had potentially been archived at this UMC. This revelation was concerning, as it is widely understood that signed informed consent documents had to remain in the hospital's own archives for a 15-year period and could not be stored outside the hospital without the explicit knowledge of the Board of Directors. Without explicit discussion by the Board and documentation of its consent, this practice was untenable.

The researchers, regrettably, had not taken such measures. The science coordinator realized that either she or a designated monitor needed to meticulously review every detail of locally initiated research subject to the WMO with the researchers. Despite the latter having completed training in and passed the exam for Good Clinical Practice (GCP), effective implementation of GCP principles in practice required the ongoing support of the hospital.

The science coordinator remains optimistic, recognizing that the insights gained from the inspection were valuable and needed to be shared with fellow researchers, colleagues and the Board of Directors within her own organization, as well as with the STZ. She believes that the chosen approach, supported by the Board of Directors and aimed at harnessing the potential of mutual learning among peers, is the right one. In her view, ensuring and enhancing the quality of medical research is an ongoing and continuous endeavour.

Forthcoming steps involve developing a short-term action plan to address the Inspectorate's immediate requirements and discussing a draft version of this plan with the Board of Directors. Looking ahead, the objective is to establish and implement a digital system that can ensure the integrity of data by facilitating the collection, management, and sharing of medical research data, all tailored to the specific needs of the hospital. A further aspiration is to foster collaboration with other hospitals in achieving consistency in good research practices.

The illustrative case shows that the landscape of medical research comprises diverse stakeholders in both the public and private sector. It highlights specific social dynamics, including the interaction between the Board of Directors and the science coordinator in shaping and organizing good clinical practice. A monitoring system is necessary within the hospital and there is a degree of flexibility in how it can be structured. Additionally, the case underscores the engagement of researchers operating across various hospitals and working in close collaboration on research. Finally, the illustrative case demonstrates the interactions between the hospital and the IGJ, which is responsible for supervising the proper conduct of medical research.

Although not explicitly addressed in the illustrative case, numerous other relationships are also at play. These include interactions among various public supervisory bodies such as the CCMO and the Medicines Evaluation Board (CBG). Furthermore, relationships between researchers and the pharmaceutical industry come into play, particularly in the context of clinical trials involving medicinal products.

Finally, the landscape of medical research in the Netherlands is undergoing a transformation, with a notable concentration of activities in UMCs and, increasingly, in non-academic teaching hospitals. One of the challenges within the regulatory regime, which encompasses legislation and a structured system of supervision, is the increasing scope for multicentre research. As demonstrated in the illustrative case, the Board of Directors and the scientific coordinator of the teaching hospital have made efforts to become an attractive research partner for multicentre research. These efforts include ensuring compliance with legal requirements and codes of conduct.

In the following sections, I explore various aspects of medical research. This includes examining the roles of values in regulating medical research, the landscape of public supervision and the conduct of medical research. Additionally, I delineate the theoretical framework, overall purpose and research questions, and methods employed. Finally, I outline the structure of this thesis.

What do we know about the role of values in regulating medical research?

The history of medical research exposes the intrinsic relationship between regulation and values in protecting research participants and guaranteeing the credibility and societal value of research results. An important milestone in this historical trajectory is the establishment of the Nuremberg Code in 1947, prompted by the reprehensible experiments conducted by German physicians during the Second World War (Vijayananthan & Nawawi, 2008). This code underscored the necessity of grounding human research in scientific principles and ethical values, emphasizing voluntary consent and the protection of participants (Otte et al., 2005). Similarly, the Declaration of

Helsinki, introduced by the World Medical Association in 1964, delineated ethical principles for medical research involving research participants (World Medical Association, 2013). Addressing global disparities in Good Clinical Practice (GCP) for clinical trials involving medicinal products, the International Conference for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) released the ICH Guidelines: Topic E6 Guideline for GCP in 1996. Compliance with this guideline ensures the protection of participants' rights and the credibility of clinical trial data (European Medicines Agency, 2002).

These historical foundations influence contemporary guidelines and offer insights into several crucial aspects, such as the interaction between regulatory regimes and key values in shaping medical research practices. Additionally, current regulations and policies serve as corrective measures derived from past tragedies (Bansal et al., 2015), illustrating the dual nature of regulation: on the one hand, it aims to protect research participants and uphold ethical values, while on the other, it endeavours to enhance the quality and outcomes of medical research through scientific values (data integrity and reliable results).

The Dutch legislative landscape reflects these historical developments. The establishment of the WMO was prompted by discussions in the House of Representatives about the status and rights of research participants.[4] In 1985, a preliminary version of the law stipulated that medical experiments involving humans required explicit authorization from a review committee. However, it was not until 1998 that the Dutch legislature officially enacted the WMO, which came into effect in 1999. This law emphasizes the safeguarding of individual rights, privacy and autonomy, echoing the international response to unethical experimentation that resulted, for example, in the Nuremberg Code.

[4] Tweede Kamer der Staten-Generaal. (1983). Patiëntenbeleid. Brief van de Staatsecretaris van Welzijn, Volksgezondheid en Cultuur. Vergaderjaar 1982–1983 kamerstuk 16 771 nr. 14.

The WMO serves a dual purpose: safeguarding research participants by upholding ethical values, and enhancing research data quality through scientific rigor (Van Wijmen, 1998). Informed consent and a favourable review by an accredited review committee (MREC) are mandated, while the establishment of the CCMO has further enhanced supervision and guidelines for medical research (Brouwer de Koning-Breuker, 2000). To ensure compliance with the stipulations of the WMO, responsibility for supervising ongoing medical research is entrusted to the IGJ (Grit & Van Oijen, 2015).

This legislative landscape is also influenced by EU legislation, which is becoming increasingly pivotal (Timmers et al., 2023) for the incorporation of key research values. The European Clinical Trials Directive 2001/20/EC (CTD),[5] meant to standardize and harmonize human medicinal research practices across Europe (European Commission, 2009), came into force in 2006. The Dutch government adopted a pragmatic approach to this EU directive by amending the WMO in 2006 (Breuker, 2005), with an additional section (5a) pertaining to scientific research involving medicinal products also being introduced (Tweede Kamer, 2005; Breuker, 2005). Ultimately, the directive was replaced in 2022 by the EU Clinical Trial Regulation 536/2014 (CTR).

The Netherlands was at the forefront of European nations in regulating medical research involving human participants (Grit & Van Oijen, 2015) in order to safeguard key ethical and scientific values. Given the country's long-standing legislative framework and system for reviewing and supervising medical research, I have focused my research on this area. My interest lies in understanding how actors, situated within various environments, navigate the ongoing dynamics, such as EU harmonization efforts. My research focuses on the enactment of rules by different actors in order to examine their 'own interpretations of their *beliefs and practices*' (Rhodes, 2012, p. 40) that they perform to ensure key values. I believe that merely converting values into regulations is insufficient; a governance perspective highlights all the other

[5] European Parliament and of Council of the European Union. (2001). Directive 2001/20/EC of the European Parliament and the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. *Official Journal of the European Communities, L121*(May), 34-44.

governing work performed to safeguard key values in practice, such as aligning the Dutch system with the new requirements of the EU or developing a monitoring system. By delving in this thesis into the institutional work being undertaken by actors, I can unravel the complex interaction between actors, institutions and practices within the Dutch medical research context and examine how they uphold ethical and scientific values. To do this, I explore the realms of public supervision and medical research, along with the actors involved in these processes.

What do we know about the landscapes of public supervision and medical research?

The landscape of public supervision (national level)

This thesis takes a distinct approach to the term 'supervision', opting not to interpret it solely as state supervision carried out by the IGJ. Instead, it employs a governance perspective that encompasses a wide range of supervisory activities and the broader context of various supervisory actors (Legemaate et al., 2013; Wetenschappelijke Raad voor Regeringsbeleid, 2013). This approach denotes a regulatory or supervisory strategy that not only accentuates the assurance of compliance but also the establishment of a checks-and-balances system to maintain an equitable and transparent distribution of responsibilities and supervisory instruments among different stakeholders. It serves as a foundation for understanding how different actors contribute to the supervision of medical research, ultimately shaping ethical and scientific values in the process.

In the Netherlands, ethics committees were established in the 1970s to pre-evaluate the suitability of medical experiments involving humans (Bergkamp, 1989). Despite limited government engagement in supervising research involving human participants at that time, the first research ethics committee was established at the Academic Hospital and Medical Faculty of Leiden University in 1976 (Jacobs, 2021). At the time of the WMO's introduction in 1999, approximately 150 review committees were operating without official government directives (Boer, 1989). Over time, this number declined to the present count of 13, primarily due to the increasing requirements of EU guidelines, regulations, national directives, and CCMO guidelines.

Moving forward, the Dutch system reveals significant tensions between different governance levels. While many other EU countries have embraced a centralized review system, the Netherlands maintains a decentralized model incorporating regional review committees (MRECs), mostly linked to one or more hospitals, and the CCMO, which acts as a review committee in specific cases as stipulated by the WMO. Additionally, several central authorities (CCMO, CBG and IGJ) are integrated into this framework.

The decentralized system is advantageous in that committee members are closely aligned with practical expertise, allowing them to offer advisory support to research applicants. One notable drawback, however, concerns the impartiality of review committees when evaluating applications from colleagues within their own organizations (Grit & Van Oijen, 2015; Timmers et al., 2023).

Review committees also play a role in supervising ongoing investigations but share this responsibility with the IGJ. In international terms, this arrangement is distinctive, as most European countries have delegated such supervision to a single authority (Grit & Van Oijen, 2015). The IGJ, in conjunction with public law supervisory bodies, i.e. the CCMO, MRECs, and CBG – responsible for registration – collectively assume responsibility for publicly supervising medical research and clinical trials (Grit & Van Oijen, 2015). How this intricate structure operates in practice and how the MRECs, CCMO, and IGJ interlink are questions that I explore in this thesis.

Below, I focus on the actors who conduct medical research in an evolving landscape.

The landscape of medical research

Prior to the 1980s, clinical research was conducted on relatively limited scale in the Netherlands (Jacobs, 2021). During that era, international pharmaceutical companies in particular permitted physicians to enrol patients in clinical trials in exchange for financial incentives or valuable gifts (Jacobs, 2021). The call for protective regulations (the codification of ethical values) gained prominence when the focus of scientific research shifted from fundamental to more applied-research (Stukart et al., 2014; Grit & Van Oijen, 2015).

In the realm of research governed by the WMO, sponsors assume multifaceted roles across different levels of governance. The sponsor, typically a legal entity, bears responsibility for initiating, managing, or financing the research. In the context of sponsored research, this role is often carried out by pharmaceutical companies, which may engage Contract Research Organizations (CROs) to assist, and frequently have a global reach. In the Netherlands, approximately 40 companies involved in drug and vaccine development are affiliated with the Association for Innovative Medicines, representing a sector marked by innovation and knowledge-intensive efforts and employing about 65,000 individuals, including 7,800 in clinical research (Dutch Association for Innovative Medicines, 2021). Moreover, the Netherlands boasts over a hundred active CROs, with about 40 being associated with the Association of Contract Research Organizations in The Netherlands (ACRON).

For pharmaceutical companies and CROs, adhering to national and international regulations, ensuring data integrity, and avoiding errors in clinical research stand as crucial imperatives. Hence, studies by pharmaceutical companies or CROs are meticulously monitored from their inception, with pre-visit audits, investigators' meetings, MREC approvals and other systems being employed to ensure the accuracy of data generated during clinical trials. International pharmaceutical companies and CROs are supposed to align with the ICH GCP guideline[6] as an international quality standard.

Furthermore, in investigator-initiated trials, hospital Boards of Directors (BoD) assume the role of sponsors, particularly with regard to feasibility assessment and quality management. The WMO has prompted deeper involvement of hospital BoDs in the research process. A CCMO guideline from 2001 requires the BoD to issue feasibility statements for (multicentre) clinical research involving medicinal products. Enforcement of this guideline led to

[6] International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). (1996). ICH harmonized tripartite guideline. Guideline for good clinical practice: Consolidated guideline; E6(R1), 10 June.

lengthier assessment periods and redundant resubmissions to local MRECs, however, and so subsequent revisions have streamlined BoD activities, with the most recent guideline applying from 31 May 2023[7].

The landscape of hospital systems in the Netherlands encompasses three tiers: general hospitals, non-academic teaching hospitals, and UMCs. The majority of Dutch medical research is conducted in UMCs and non-academic teaching hospitals, both of which have undergone mergers and structural changes in recent years, reducing their overall numbers. Non-academic teaching hospitals have also now ventured into research, with 26 out of approximately 80 general hospitals prioritizing research in specific disease areas within their organizational structure. The Netherlands Federation of University Medical Centres (NFU) is tasked with coordinating research activities within UMCs, whereas the Association of Top Clinical Teaching Hospitals (STZ) fulfils this role for teaching hospitals. Although research collaboration has become standard practice, particularly between UMCs and teaching hospitals, there is little understanding of the impact of this collaboration and the strategies involved in achieving it. These aspects are therefore another focal point of enquiry in this thesis.

Hospital physicians play a pivotal role in clinical trials due to their expertise in recruiting and treating patients and prescribing medicinal products. Their dual role as physicians and researchers can give rise to conflicts of interest, however. In the contemporary landscape, professionals must navigate a complex interplay of national and international regulations, coupled with hospital-specific codes of conduct. The potential for conflicts of interest is particularly pronounced in research funded by the pharmaceutical industry, impacting data integrity (Davidson, 1986; Bero et al., 1992; Cho & Bero, 1996; Wahlbeck & Adams, 1999; Kjaegard & Als-Nielsen, 2002; Yank et al., 2007; Sismondo, 2008). This dynamic can be reversed in investigator-initiated trials, where the researcher enjoys a higher degree of autonomy in determining research priorities. Here, however, unchecked personal interests could compromise researcher independence and, consequently, ethical and

[7] Staatscourant (2023). CCMO-richtlijn Toetsing geschiktheid onderzoeksinstelling, nr. 15319, 31 mei.

scientific values. The adequacy of corrective mechanisms is a matter of concern, particularly as monitoring of investigator-initiated trials is often insufficient or non-existent, further complicated by a lack of funding (European Science Foundation, 2009). Given the increased focus on monitoring systems, including those involving employee monitors, I investigate the development of these quality systems within UMCs and teaching hospitals in this thesis.

In the following I explore the theoretical perspectives that underpin medical research governance and institutional viewpoints. My exploration has helped me understand the work of actors across diverse contexts – work that I have found is crucial for ensuring the integrity and ethical conduct of medical research amid diverse challenges.

The theoretical lenses in this thesis

Defining governance in medical research

Throughout this thesis, the focus at each regulatory level is on the actions actors undertake to interpret and implement regulations, in conjunction with ethical and scientific values. These values are translated into practical measures but what they emphasize may vary at each governance level.

I employ an interpretative approach to governance, which Rhodes refers to as 'the third wave of governance: interpretating the changing state. This approach represents a shift of topos from institutions to *meanings* in action. It explains shifting patterns of governance by focusing on the actors' own interpretations of their *beliefs and practices*' (Rhodes, 2012, p. 40). This is a bottom-up approach, examining the practices of actors across diverse contexts. The objective is to uncover their actions and associated beliefs, especially in response to dilemmas or internal or external challenges. It underscores that governance is evolving continually in everyday practices and emphasizes that institutions are not static but rather outcomes of ongoing institutional work that are constantly reshaped through iterative processes.

To elucidate the concept of governance in medical research, I initially employ the general definition of governance by Torfin et al. (2012) in Ansell & Torfing (2022). In the *Handbook on Theories of Governance*, Ansell and Torfing (2022) reflect on the different definitions of governance as given by Kooiman (1993), Jessop (1998), Bevir and Rhodes (2003), and the World Bank (2007). These authors define governance too narrowly or leave the definition open to an endless number of contextual interpretations. To avoid these pitfalls, governance is defined generically as 'the process of steering society and the economy ("how") through collective action and in accordance with common goals ("what")' (Torfing et al., 2012, in Ansell & Torfing, 2022, p. 3).

A broad definition of governance is very useful when examining how various interconnected actors in medical research, such as researchers, sponsors and supervisory bodies, implement diverse governance actions to maintain ethical standards and scientific integrity. This approach also elucidates how these values shape actors' attitudes, behaviours, and interactions in the field. In essence, these actors are guided by a shared commitment to navigating complex ethical dilemmas and scientific challenges. By focusing on the governance dimension in medical research, this thesis aims to uncover how actors interpret and enact governance mechanisms to ensure key values in their daily practices. Exploring these interactions and decisions can lead to a deeper understanding of the governance dynamics within the medical research landscape, thereby helping to promote responsible and ethical research practices.

Institutional theories

In this thesis I explore the governance actions of actors using institutional theories as my modes of analysis. The concepts of institutional work and institutional change are particularly constructive for analysing the dynamic tension between stability and flexibility in governance systems because they focus on the interactions between actors and institutional structures (Beunen et al., 2017). Moreover, a central focus in institutional change scholarship is the interplay between actors and *governing* structures (Mahoney & Thelen 2010; Lawrence, Suddaby & Leca 2009; Bettini, Brown & De Haan 2015), especially in multilevel governance systems of medical research. My aim in this thesis is to use new ways of conceptualizing this interplay so as to analyse

institutional change in different medical research settings where ethical and scientific values are developed and assured over and over again (Beunen & Paterson, 2019).

The concept of 'institutional work' offers a valuable analytical lens for understanding the processes and mechanisms that drive institutional change within the intricate, multilayered governance systems of medical research. Coined by Lawrence and Suddaby (2006), institutional work refers to the actions through which actors create, maintain, or disrupt institutional structures. In each governance system, actors continuously participate in actions and interactions that can preserve, modify, contest, or even replace institutional meanings and significance (Beunen & Paterson, 2019). Institutions also embody shared beliefs, in this thesis referred to as ethical and scientific values. The interpretative approach to governance, as delineated in Rhodes' third wave (2012), emphasizes the critical task of translating these universally acknowledged key values into tangible actions. This perspective underscores a decentralized analysis of actor interactions and their influence on shaping the interpretation of practices, thereby offering valuable insights for policymakers (Rhodes, 2021). Moreover, given the complexity of multilevel governance systems, the process of institutional work as it pertains to any institutional structure is intricately linked to dynamics and changes in other segments of the governance landscape. Thus, institutional work must be understood within its specific contextual parameters (time, place, scale), which are embedded within broader, dynamic governance and political-economic contexts (Beunen & Paterson, 2019).

For this thesis, I have extended the definitions of institutional work in the manner by Beunen and Paterson (2019). In the original definition, institutional work does not take nonpurposive action into account (i.e. unconscious actions taken by actors, which nevertheless may have a significant effect), nor specifically considers its actual effects on the institutional structure in question. According to Beunen and Patterson, however, such nonpurposive actions and effects are of importance too. For example, practitioners' goals might not be to alter institutions, but in their efforts to get things done – i.e. working with novel research methodologies or setting up new organizational formats for doing research – they

nevertheless engage in institutional work. These actors are not deliberately trying to change or create institutions, but are doing so more or less along the way. Institutional work should therefore encompass both the actions taken by actors and the resulting (partly unintended) effects, and can then be defined as those actions through which actors attempt to, or in effect do, create, maintain, or disrupt institutional structures (Beunen & Paterson, 2019).

Mahoney and Thelen (2010) argue that we need to look beyond either stability or radical change and focus on gradual and ongoing forms of institutional change. They contend that institutional rules are rarely unambiguous and that this ambiguity—which can come from conflicting values and goals—provides room for flexibility and manoeuvring by actors, as rules and regulations are never fully able to master the complexity and variety of the medical research field that they are meant to control. This can lead to gradual change over time as such rules are reinterpreted, recast under new circumstances, or otherwise contested. Even though this approach focuses on 'gradual' change, it also points out that gradual change may nevertheless lead to broader transformative change over time (Streeck & Thelen 2005; Beunen & Paterson, 2019). For this reason, I emphasize ongoing forms of institutional change in practice that result from the actions of actors at the various governance levels.

In this thesis, boundary work is considered a specific type of institutional work that involves creating, maintaining or interrupting boundaries between organizations or domains. As defined by Gieryn (1983), it refers to actors' efforts to establish, expand, reinforce, or undermine these boundaries. More in detail, I employ three organizational boundary concepts—'identity,' 'competence,' and 'power'—as presented by Santos and Eisenhardt (2005). This framework provides a structure through which I can illustrate how two non-academic teaching hospitals initiate and enhance research collaborations with academic partners for their highly specialized care and medical research domains.

In the course of writing the discussion section of this thesis, I identified three governance mechanisms: 'rules', 'room', and 'responsibilities'. The first mechanism, as explained in the role of values in regulating medical research, involves regulations, laws, guidelines, codes of good conduct, standards, and funding requirements. The second mechanism, 'room', grants actors the flexibility to make context-specific judgments and decisions, fostering innovation and adaptation within the research environment. This flexibility is closely linked to actors' drive for change, learning, and experimentation, as discussed by Duit and Galaz (2008). The third mechanism revolves around the assignment, distribution and adoption of 'responsibilities', a crucial aspect in the governance of the medical research system, as detailed in the landscapes section. Supervision plays a pivotal role in medical research and coordination work is often required to ensure proper allocation of roles. For example, as highlighted in the illustrative case, the Board of Directors act as a sponsor, bearing responsibility for establishing and maintaining systems and procedures for quality assurance and quality control in investigator-initiated research. Actors within the medical research field are tasked with various and sometimes shared responsibilities or may adopt responsibilities due to dynamic circumstances. In practice, these three governance mechanisms often intersect and interact, reflecting the dynamic nature of both research environments and legislation. While rules provide structure and guidance, room allows for creativity and exploration, and responsibilities delineate the duties and obligations of actors involved.

In the discussion section of this thesis, I examine how actors negotiate and navigate these governance mechanisms to ensure the ethical conduct and integrity of medical research, their aim being to achieve a certain level of resilience in review or supervision practice. By exploring the interplay between rules, room and responsibilities, I attempt to shed light on the dynamics of institutional work within the Dutch medical research context and the implications for governance practices.

What do we still need to know? Overall purpose and research questions

In the realm of medical research, the intricate interplay among diverse actors and the evolving challenges within a multilevel governance framework require a deeper understanding of the work that actors perform to promote and safeguard ethical and scientific values. This thesis examines the (proactive) activities and measures adopted by actors engaged in institutional work to navigate such dynamic challenges. By delving into the complexities involved, I illuminate the multifaceted processes that help protect research participants and scientific rigour in practice.

Research aim

The primary objective of this research is to expand our understanding of institutional work undertaken by various actors to effectively respond to the ever-changing challenges and complexities in medical research governance. This investigation is directed towards uncovering the actions, strategies, and adaptations that actors engage in, both within and across different levels of governance. Through this exploration, I seek to unravel mechanisms that safeguard ethical and scientific values, enabling a more comprehensive appreciation of the regulatory dynamics in medical research.

Research question

The research question of this thesis is:
What forms of institutional work are undertaken by public and private actors to address dynamic challenges within the multilevel governance structure of medical research in order to ensure the protection of research participants and scientific integrity and to attain research impact?
By meticulously examining the activities and strategies employed by actors involved in the governance of medical research, I aim to contribute to a nuanced understanding of how ethical and scientific values are upheld and promoted within the domain of medical research governance.

This thesis will answer the following sub-questions (see Table 2).

Table 2 Overview of sub-questions

No.	Sub-question
1.	How do different actors respond to changes originating from EU regulation within layered legislative systems?
2.	How do public supervisors of ongoing clinical trials in the Netherlands respond to the external challenges in the Dutch regulatory regime?
3.	How are systems that ensure the data quality in investigator-initiated trials organized in Dutch hospitals?
4.	What is the impact of research collaboration on medical research output in Dutch hospitals and how do TopCare hospitals initiate and improve productive research collaborations?

Methods

This empirical research employs a variety of qualitative and quantitative methods to examine the efforts undertaken by actors to address dynamic challenges to the ethical and scientific values embedded in legislation and regulations across various levels of medical research governance. Triangulation in research entails utilizing multiple methods or data sources to obtain a comprehensive understanding of phenomena (Patton, 1999). The fundamental premise behind triangulation is that the limitations of each data source are mitigated when the sources are used in conjunction. For instance, when data collection is conducted through interviews, the research then depends to a significant extent on the viewpoints, perspectives, and recollections of the respondents. Confidence in the findings can be improved by combining interview data with other forms of data, such as observations, document analysis or surveys. This underscores the importance of employing multiple sources of information to generate more robust and reliable research outcomes (Klettner et al., 2010).

Table 3 summarizes the research techniques employed to address the various research questions. Consistent with Rhodes' interpretative approach, which focuses on decentralized governance analysis, data collection primarily relies on qualitative research methods: collecting stories from the actors involved in safeguarding ethical and scientific values in medical research (Rhodes, 2012).

Table 3 Overview of qualitative, quantitative and previous research

Publication	Theme/subject	Qualitative research	Quantitative research
Health Policy (HP) (2017) Chapter 2	Public supervision of clinical trials	Document analysis Interviews (n=33) Observations (n=4)	
PLOS ONE (2020) Chapter 3	Public supervision of ongoing clinical trials	Document analysis period 1999-2018 Interviews (n=27)	
Accountability in Research (2022) Chapter 4	Data quality in investigator-initiated trials	Interviews (n=26) Observation (n=5)	Online survey of BoD in 2017
Health Research Policy and Systems (HRPS) (2024) Chapter 5	Research impact in medical research through collaboration across organizational boundaries	Document analysis Interviews (n=27)	Bibliometric analysis

To ensure the protection of participants involved in medical research and to uphold the accuracy and reliability of data, the practice of medical research in the Netherlands is governed by legislation and a structured system of supervision and review, collectively forming the Dutch regulatory regime. The practice of medical research operates within a multilevel governance framework.

In this thesis, I investigate four distinct governance levels in this framework as illustrated in Table 4, each involving various categories of actors. At the supranational level (a), the European Union has attempted to harmonize rules and regulations governing clinical trials across its Member States. This has led to a complex process of implementation for the Netherlands due to its pre-existing regulatory regime, posing challenges at the national level (b) in the supervision of clinical and ongoing trials. Subsequently, the Dutch Propatria incident affected Dutch hospitals, which are responsible for upholding data integrity in investigator-initiated trials at the local level (c). Finally, a new programme called TopCare was launched in 2014 in which three non-academic teaching hospitals received funding from the Ministry of Health to conduct medical research in combination with highly specialized care.

These Dutch hospitals play a pivotal role in initiating and enhancing productive research collaborations within the realm of medical research, with implications for the national and local levels (d).

Table 4 Four different governance levels of medical research

Level	The studied governance levels of medical research
[a] Supranational	EU harmonization and institutional change and institutional work in the regulation of Dutch clinical trials
[b] National	Challenges in supervision of ongoing trials
[c] Local	Data quality in investigator-initiated trials in Dutch hospitals
[d] National/local	Research output and impact in Dutch hospitals, and productive research collaboration in Dutch TopCare hospitals

The empirical research is based mainly on three research projects supplemented by additional data collection and/or previous studies.

1. A research project focusing on the supervision of medical research, subject to the WMO as part of the 'Academische Werkplaats Toezicht (AWT)' (period: 2013-2014) (Grit & Van Oijen, 2015).
2. A research project on monitoring practices in Dutch UMCs and teaching hospitals (period: 2014-2018).
3. The TopCare programme which allocated funding to three non-academic teaching hospitals for a four-year period (2014-2018). The objective of the programme was to conduct medical research in conjunction with providing highly specialized care.

The empirical study in Chapter 2 focuses on the practical implementation of a new EU directive (the CTD) within the current Dutch regulatory system and specifically examines public supervision. This study is based entirely on the data collected during the AWT project, including interviews and observations, complemented by document analysis.

Chapter 3 analyses the response of public supervisory bodies to challenges such as the CTD and critical reviews and incidents. This study is based in part on the AWT project and is complemented by document analysis and interviews conducted between December 2013 and May 2018. In both Chapters 2 and 3, the goal is to explore the concept of 'law in action' (Versluis, 2007) or 'meaning in action' (Rhodes, 2012) by assessing how rules are

translated into or interpreted in everyday practices (Klettner et al., 2010). The empirical studies in these chapters focus on the experiences and viewpoints of actors involved in the supervision of (ongoing) clinical trials. This includes both national and international public supervisory bodies, inspectors, hospital staff, and Boards of Directors.

Inspiration for the research in Chapter 4 can be traced back to the AWT project. This project raised concerns about the monitoring practices for investigator-initiated trials (IITs), which, when in place, often do not function optimally (European Science Foundation, 2009). I examine how such actors as the staff and Boards of Directors of UMCs and teaching hospitals, the IGJ and CCMO respond to (corporate) governance in medical research to ensure data quality in investigator-initiated trials. Qualitative and quantitative research methods were employed, as well as data from a prior study conducted in 2003 among BoDs (see Table 3).

Chapter 5 focuses on research impact and research collaboration. I had the opportunity to use the bibliometric analysis and interview data from the TopCare programme gathered between 2014 and 2018. Additionally, I conducted a bibliometric analysis of the publications of 28 teaching hospitals and eight UMCs in the Netherlands from 2009 to 2018. This study utilized data obtained from the Centre for Science and Technology Studies' (CWTS) in-house version of the Web of Science (WoS) database. Moreover, I collected ethnographic interview data (n=27) from BoDs, project and programme leaders and researchers at the two TopCare non-academic teaching hospitals. This data was used to explore the boundary work done by these hospitals to initiate or improve their research collaboration with academia.

A detailed description of the research design and methodologies can be found within each chapter.

Outline of the thesis: Dynamic challenges in different governance practices

As emphasized by Beunen and Patterson (2019), the process of institutional change occurs within a specific governance context, characterized by unique constellations of actors and existing institutions (Bontje et al., 2019). In pursuit of the research aim articulated in this thesis, I have undertaken an in-depth analysis of governance practices in medical research across four distinct levels. This involved conducting four separate research studies in collaboration with authors from within and outside the Erasmus School of Health Policy and Management. These studies employ a variety of research methods, as outlined in the methods section.

Chapter 2. Dynamic cycle of institutional change and institutional work due to the EU's harmonization efforts

As previously mentioned, the legal framework governing clinical research involving human participants is a composite of national and international provisions, each with its own legal status and enforceability, constituting a complex legal environment for supervision. In this chapter I highlight why the Dutch legislature has chosen to retain as much of the existing Dutch system of review and supervision as possible while implementing new EU regulations. I also examine the consequences of such a complex legal system for the Inspectorate and other public supervisory bodies from the perspective of institutional changes and institutional work.

Chapter 3. Institutional work in response to external challenges in public supervision of ongoing clinical trials

Even with an approved research protocol, ensuring the protection of research participants remains an ongoing challenge. Supervision therefore extends beyond the pre-research phase and persists throughout the research process (Van Oijen et al., 2016). In this chapter, I unfold the work undertaken both by public entities (such as IGJ, CCMO/MRECs and CBG) and by private actors (including hospital BoDs, researchers, and monitors) to safeguard the well-being of research participants and to maintain research integrity and quality during the execution phase of medical research (Van Oijen et al., 2016). Focusing on external challenges, such as EU harmonization, incidents and

other triggers, allows us to identify potential discrepancies between legal regulations and the practical implementation of ongoing trial supervision. We also explore the reasons behind a potential collaboration and the complementary aspects as well as the disparities, gaps and conflicts arising from the involvement of multiple actors in the supervisory process. We examine the strategic positioning of IGJ and other supervisory bodies within this framework, as a misalignment between these actors may lead to overlaps or deficiencies (Wetenschappelijke Raad voor Regeringsbeleid, 2013).

Chapter 4. Working on ensuring data quality of investigator-initiated trials in hospitals

The OECD report *Recommendations on the Governance of Clinical Trials* (2013) mentions a decline in the number of clinical trials, particularly those initiated by academic researchers for non-commercial purposes. Additionally, the report highlights concerns related to infrastructure, database management, quality assurance and monitoring, as these components are found to be suboptimal in these trials. My investigation centres on BoDs, which act as a sponsor of non-commercial investigator-initiated trials, and their involvement in quality assurance activities, particularly in monitoring. This role calls on them to allocate sufficient time, resources and capacity to facilitate effective research monitoring. In this chapter I examine how hospitals deal with their quality assurance task and how they may encounter challenges due to constraints in financial resources.

Chapter 5. Boundary work to improve productive research collaboration and to achieve research impact

The landscape of medical research governance in the Netherlands is undergoing significant transformations. Historically concentrated within public academia, specifically UMCs, the scope of medical research is expanding to encompass non-academic teaching hospitals. Furthermore, the TopCare programme in 2018 prompted a significant push towards medical research in three teaching hospitals, as it augmented funding to them to support clinical research alongside highly specialized healthcare services. Despite the increasing emphasis in the Netherlands on research collaboration between UMCs and non-academic hospitals, its impact and the strategies essential for effective collaboration are little understood. To address this gap,

I conduct a quantitative analysis exploring research collaboration across Dutch hospitals and specifically within TopCare hospitals. Additionally, to gain a deeper understanding, I employ a qualitative approach to examine how two TopCare hospitals foster and strengthen their research collaboration with academia. In particular, I examine the organizational boundary work undertaken by these hospitals during the TopCare programme with a model developed by Santos and Eisenhardt (2005).

Chapter 6. Discussion and Conclusion

I begin by outlining the main findings of each sub-question, the aim being to synthesize the results into a conceptual model that answers the main research question. This conceptual model shows how the institutional work that actors undertake to implement the three interconnected governance mechanisms, i.e. rules, room and responsibilities, can lead to a certain degree of resilience. This model can be applied to the review and supervision of medical research settings, where actors have overlapping responsibilities. Additionally, I evaluate the theory and methodology, make recommendations for further research, and revisit the illustrative case presented in the introduction. Finally, I formulate recommendations for the governance of medical research.

Chapter 2

Dynamic cycle of institutional change and institutional work due to the EU's harmonization efforts

This chapter has been published as: Van Oijen, J. C. F., Grit, K. J., Van de Bovenkamp, H. M., & Bal R. A. (2017). Effects of EU harmonization policies on national public supervision of clinical trials: A dynamic cycle of institutional change and institutional work. *Health Policy, 121,* 971–977. https://doi.org/10.1016/j.healthpol.2017.08.008

Abstract

Background

The EU Clinical Trials Directive (EUCTD) and the EU Clinical Trials Regulation aim to harmonize good clinical practice (GCP) of clinical trials across Member States. Using the Netherlands as a case study, this paper analyzes how endeavours to implement the EUCTD set in motion a dynamic process of institutional change and institutional work. This process lead to substantial differences between policy and actual practice; therefore, it is important to learn more about the implementation of harmonization policies.

Methods

Relevant documents, such as legal texts and previous research, were analyzed. Interviews were conducted with stakeholders in clinical trials and inspectors from (inter)national supervisory bodies (n=33), and Dutch Health Care Inspectorate inspections were observed (n=4).

Results

Dutch legislators' efforts to implement the EUCTD created a new level of governance in an already multilevel legislative framework. Institutional layering caused a complex and fragmented organizational structure in public supervision, leading to difficulties in achieving GCP. This instigated institutional work by actors, which set in motion further incremental institutional change, principally drift and conversion.

Conclusions

Harmonization processes can create dynamic cycles between institutional change and institutional work, leading to significant divergence from the intended effects of legislation. If legislation intended to strengthen harmonization is not carefully implemented, it can become counterproductive to its aims.

Keywords

Clinical trials; Good clinical practice (GCP); Harmonization; Institutional change; Institutional work; Public supervision

Introduction

Clinical trials rely on human subjects to participate in research. Good clinical practice (GCP) is considered essential in order to secure the protection of human subjects and the validity and integrity of data. The Clinical Trials Regulation EU no. 536/2014[8] to be enacted in 2018 will replace the EU Clinical Trials Directive 2001/20/EC (EUCTD)[9] (European Parliament and of the Council of the European Union, 2001). The European Union (EU) has taken different initiatives to harmonize the way clinical trials are conducted across Member States. However, in practice, the intended effect of the EUCTD to harmonize the international regulatory framework for clinical trials has not been fully achieved (The Academy of Medical Science, 2011; European Commission, 2009; European Forum for Good Clinical Practice, 2009; Hernandez et al., 2009; Gluud et al., 2012). The new Regulation aims to create an environment that is favourable for conducting clinical trials for all EU Member States (European Commission, 2014). It provides measures to cut red tape, simplify the rules, and ensure that rules for conducting clinical trials are consistent throughout the EU (European Commission, 2014).

Institutional change takes place whenever EU legislation is implemented in Member States, because the EU legislation must be translated into a national legislative framework and adapted in local practices. Accordingly, differences in legal practices are allowed to some extent; but, as public supervision of clinical trials remains the responsibility of Member States, this could create tension between the new EU regulation and existing national institutions. It therefore remains crucial for researchers to investigate how legislation is implemented and interpreted by actors in practice. The actors' implementation and interpretation largely determine how institutional

[8] European Parliament and of the Council of the European Union. (2014). Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive /20/EC. *Official Journal of the European Union, L158*(May), 1–76.

[9] European Parliament and of Council of the European Union. (2001). Directive 2001/20/EC of the European Parliament and the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. *Official Journal of the European Communities, L121*(May), 34–44.

change develops, and the extent to which the goal of harmonization is reached. To gain more insight into how legal endeavours for EU harmonization evolve in practice, we use theory on institutional change (Mahoney & Thelen, 2010) and the concept of institutional work (Lawrence & Suddaby, 2006).

The topic of public supervision of clinical trials gives us a generous context in which to observe the institutional change caused by harmonization attempts. In our case study, we examine the practice of public supervision concerning the approval of research proposals and protocols, and the supervision of ongoing research and multicenter trials. This article focuses on the efforts of the Netherlands to implement the EUCTD. Because the Netherlands had existing legislation concerning GCP in place before the EUCTD was introduced, as a case study, it can help us understand the possible changes that will be wrought by the new Regulation. It provides insight into the complexity of implementing EU legislation within the existing institutional practices of Member States. Using the EUCTD as a starting point, we examine institutional change and how actors influence this process through institutional work in our case study.

Theory

Mahoney and Thelen define institutions as the rules, norms, and procedures of political and social life that organize behaviour into predictable and reliable patterns (Mahoney & Thelen, 2010). By following Streeck and Thelen (2005), they identify four types of institutional change. *Layering* is a form of institutional change whereby existing institutions are not replaced, but are attached to new institutional layers, which alter the structure of the original institutions. *Drift* refers to situations in which institutions remain formally the same, but their impact changes as a result of shifts in external conditions and an absence of adjustment to them. *Conversion* describes a change in the enactment of existing rules; this can happen when the rules are imprecise and allow for significant discretion in their interpretation and enforcement. *Displacement* occurs when existing institutions are replaced by new ones. Mahoney and Thelen argue that institutional arrangements are inherently dynamic. Because rules allow room for interpretation, debate, and

contestation, institutional arrangements always represent compromises and relatively durable, but still contested, settlements (Mahoney & Thelen, 2010). Additionally, actors with different interests and perspectives can operate strategically in their institutional environment, which can instigate further incremental institutional change (Hacker, 2004; Streeck & Thelen, 2005; Mahoney & Thelen, 2010; Sheingate, 2010).

Therefore, in order to study how institutional change develops in practice, it is essential to analyze the institutional work of actors. Unfortunately, Mahoney and Thelen do not address this subject in depth (Rocco, 2014). For this reason, we use the concept of institutional work to further understand the way actors instigate incremental change. Institutional work focuses on the role of actors in creating, maintaining, and disrupting institutions (Lawrence & Suddaby, 2006; Van de Bovenkamp et al., 2017). This theory helps us better understand the practical origins and consequences of the institutional change caused by the EU's endeavours for harmonization.

By adopting Mahoney and Thelen's model and combining it with institutional work theory, we can conceptualize and analyze the changes that occurred in our case study over time. The literature on institutional change often focuses on just one of the different types of change (e.g. Van de Bovenkamp et al., 2014); however, there are also case studies of complex policy change processes that show the dynamic interaction between different types of change (e.g. Shpaizman, 2014; Barnes, 2008; Thatcher & Coen, 2008; Béland, 2007; Falleti, 2010). We want to build on the latter by exploring how harmonization policies can lead to layering, which necessitates institutional work, which in turn, causes further incremental institutional change. Such insight is important because it can help us understand complex institutional change.

Methods

Our methods were chosen for their ability to provide insight into the institutional change and institutional work caused by the implementation of the EUCTD as a new level of legislation in the existing multilevel structure of public supervision in the Netherlands. We used qualitative research methods

to explore this process, and how it could lead to disparity between EU law and national institutional practices. To begin with, we analyzed relevant documents, such as legal and policy texts, and previous research on the conduct and supervision of clinical trials. To understand processes of institutional change, our research work was first oriented to discover how both rules and institutions were formulated before and after the harmonization process; for this reason, it was important to also study the history of legislation.

To be able to discern the relationship between institutional work and incremental institutional change, we investigated how legislation is implemented and interpreted in practice at EU and national levels. We interviewed inspectors from the Dutch Healthcare Inspectorate (n=8), other Dutch public supervisory bodies and the European Medicines Agency (EMA) (n=13); as well as stakeholders in clinical trials (n=12) who have experience in the application of institutional rules or are involved in public supervision, e.g., professional and interest groups. We paid particular attention to the position of globally oriented private actors, such as sponsors and contract research organisations (CROs), who work across many national institutional frameworks. These interviews were conducted between December 2013 and July 2014. They were semi-structured and focused on the actors' experiences with the institutional arrangements of the supervision of clinical trials. The interviews were recorded and fully transcribed, and the processed data were submitted to the respondents for member check.

In addition to the interviews, we attended four inspection visits of international multicenter trials conducted by the Dutch Health Care Inspectorate. We observed how the Inspectorate supervised the cooperation between sponsors and CROs over the course of six days in January through June of 2014. Because national inspectorates or authorities need to supervise the activities of international businesses within their borders, problems may arise if the application of GCP varies between Member States. Studying this kind of supervision informed us further about the characteristics and consequences of institutional change within the context of EU legislation.

We coded and analyzed the documents, interviews, and observation notes to gain more insight into how legal endeavours to harmonize EU and national legislation evolve in practice. These different sources of data allowed for comparison and triangulation, and their qualitative nature enabled us to see tangible institutional change.

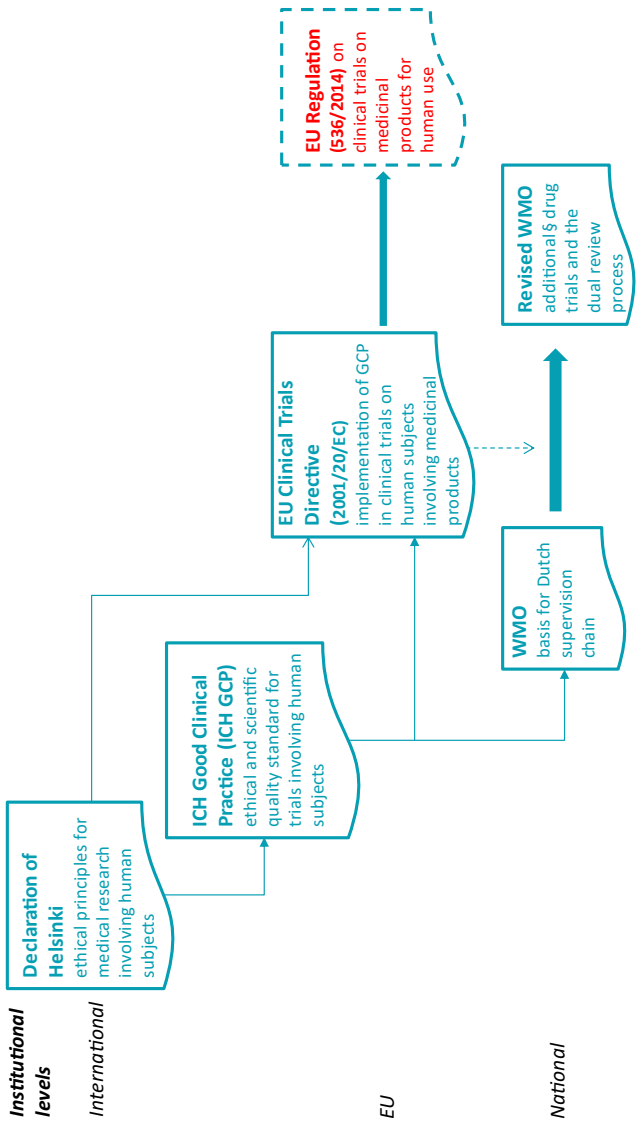
Results

The goal of our research was to examine the dynamic institutional effects of EU legislation on public supervision of clinical trials in the Netherlands. As we demonstrate below, the need to implement the EUCTD with existing legislation made layering the preferred form of institutional change. One of the consequences of layering was a complex and fragmented organizational structure of Dutch public supervision. The difficulties arising from this continue to require actors to engage in institutional work that causes further incremental institutional change. We can observe drift in the practice of supervision of ongoing trials and conversion in the international practice of multicenter trials. In the discussion and conclusion, we reflect on the consequences of these findings for the upcoming Regulation.

Institutional layering as a result of a multilevel legislative framework

This section examines the multilevel (inter)national legislative framework resulting from the EU's endeavours for harmonization. We explain how the integration of international, EU, and national institutions governing clinical trials lead institutional arrangements in the Netherlands to be amended, rather than replaced. The Dutch case can therefore be labelled institutional layering. We begin with a short historical overview of relevant international and national initiatives and legislation to demonstrate how the multilevel structure of public supervision in the Netherlands emerged.

Since World War II, international measures have been taken to protect the human rights of subjects involved in clinical trials. First, the Nuremberg Code, a set of research ethics principles for human experimentation, was established in 1947 (Annas & Grodin, 1992). Next, the Declaration of Helsinki was established for medical doctors conducting biomedical research (World


Institutional levels
International
EU
National
Declaration of Helsinki
ethical principles for medical research involving human subjects
ICH Good Clinical Practice (ICH GCP)
ethical and scientific quality standard for trials involving human subjects
EU Clinical Trials Directive (2001/20/EC)
implementation of GCP in clinical trials on human subjects involving medicinal products
EU Regulation (536/2014) on clinical trials on medicinal products for human use
WMO
basis for Dutch supervision chain
Revised WMO
additional§ drug trials and the dual review process
Prepared by
World Medical Association
International Council on Harmonization (ICH)
Dutch Ministry of Health, Welfare and Sport
European Parliament and the Council
Dutch Ministry of Health, Welfare and Sport
European Parliament and the Council
Year
1964
latest revision in 2013
1997
first adaption in 1990
1999-2005
2001-2015
2006
2018

Medical Association, 2013). It formed the basis for the ethical principles that underlie the good clinical practice (GCP) guidelines[10] (International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, 1996) that followed (see Figure 1). In an effort to overcome GCP inconsistencies between countries, the International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) was created by a steering group of representatives of the regulatory agencies and industry associations of Europe, Japan, and the US (The International Council for Harmonization, n.d.). The ICH developed a version of GCP (ICH GCP) comprising thirteen core principles. When first expounded in 1997, it was internationally recognized as best practice, but was not enforced by law (Vijayananthan & Nawawi, 2008). The Netherlands was one of the first EU countries to take the initiative of juridification when the Dutch Ministry of Health, Welfare and Sport created national legislation incorporating the ICH GCP. The Medical Research Involving Human Subjects Act (WMO)[11] established a new multilevel structure of supervision within the Netherlands. Supervision was executed at a national, centralized level by the Dutch Health Care Inspectorate, and at a local, decentralized level by a system of regional medical research ethics committees (MRECs).

International rules for the protection of clinical trial subjects and public health were largely accepted by many countries (European Commission:29), but the laws regarding the supervision of clinical trials varied significantly between them. In an endeavour for harmonization, the EU enacted the first Clinical Trials Directive (2001/20/EC) in 2001. Legally enforcing supervision of clinical trials from 2004 onwards, the Directive aimed to ensure the protection of subjects, the ethical soundness of clinical trials, and the reliability of generated data. In some Member States, the EUCTD was transposed into a completely new law; for instance, in the UK, the Medicines for Human Use (Clinical Trials) Regulations were launched in 2004, replacing existing

[10] International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). (1996). ICH harmonized tripartite guideline. Guideline for good clinical practice: Consolidated guideline; E6(R1), 10 June.

[11] Staatsblad van het Koninkrijk der Nederlanden. (1998, 161). Wet van 26 februari 1998, houdende regelen inzake medisch-wetenschappelijk onderzoek met mensen (Wet medisch-wetenschappelijk onderzoek met mensen) [Medical Research involving Human Subjects].

regulations. Other countries, such as France, Finland, Ireland, and the Netherlands, integrated the EUCTD into existing law. In the Netherlands, a new article on clinical trials was added to the WMO (2006, Articles 13a-13r)[12].

In order to provide greater protection to its subjects, the EUCTD required a clinical trial to be approved separately by both a single competent authority assessing and inspecting medical and scientific aspects, and an ethics committee (European Parliament and of the Council of the European Union, 2001, nr. 11). This encouraged a system of centralized supervision. However, the WMO (1999) had established a decentralized system in which the Dutch ethics committees, the MRECs, oversaw a combination of both ethical and medical-scientific concerns. The Netherlands chose to maintain this structure based on the political understanding that had been reached a decade before, and to maintain the expertise of the regional authority of MRECs, which were often situated near the daily working practice, and had long been the most experienced and active stakeholders in approving human research trials. The Netherlands created different competent authorities that share the responsibilities of assessment and inspection: the Dutch Ministry of Health, the Dutch Healthcare Inspectorate, and the Central Committee on Research Involving Human Subjects (CCMO) (see Table 1). As a consequence, the Dutch Ministry of Health now has the role of legislator as well as competent authority, and the organizational structure of public supervision in the Netherlands is complex and fragmented. Many of our respondents have remarked on the difficulties of this fragmented structure:

> It's all so divided in the Netherlands: Inspectorate, CCMO, the Medicines Evaluation Board. The supervisory chain is fragmented, and therefore, many parties need to work together on issues that need a quick settlement. (interview MEB policy employee)

[12] Staatsblad van het Koninkrijk der Nederlanden. (2006, 644). Wet van 30 november 2006 tot wijziging van diverse wetten op of in verband met het terrein van VWS, ten einde wetstechnische gebreken te herstellen en andere wijzigingen van ondergeschikte aard aan te brengen (Reparatiewet VWS 2006).

Table 1 Overview of the roles and responsibilities of Dutch public supervisory bodies over time

Dutch public supervisory bodies	Roles and responsibilities based on the WMO of 1999	Type of public supervisory body	EUCTD of 2001	Dutch public supervisory bodies	Supplemented roles and responsibilities based on the revised WMO of 2006
Decentralized accredited medical research ethics committees (MRECs)	"The research protocol must have been approved by a *MREC* which is competent to give such approval ..." (Article 2)	*Member States: Ethics committee*	"The sponsor of a clinical trial may not start until the *ethics committee* has issued a favorable opinion..." (Article 9)	*MREC*	"A *MREC* may suspend or withdraw its approval for a research protocol if it has well-founded reasons to conclude that continuation of the trial would lead to unacceptable risks for the subjects." (Article 3a)
Central Committee on Research Involving Human Subjects (CCMO)	"The *CCMO* monitors the activities of the *MRECs* and is empowered to issue guidelines regarding the conduct of activities they carry out in accordance with this Act." (Article 24) - Checks whether a *MREC* meets obligations (accreditation) (Article 16) - Oversees the operations of *MRECs* and can set up new directives regarding their operations (Article 24) - Act as reviewing committee for specific fields of research (Article 19)	*Competent authority*	-"...the *competent authority* of the Member State concerned has not informed the sponsor of any grounds for non-acceptance." (1, Article 9) - 'Inspection': the act by a *competent authority* of conducting an official review of documents, facilities, records, quality assurance arrangements..." (1, Article 2)	*Competent authorities: (1) Ministry of Health, Welfare and Sport, (2) CCMO*	The Ministry of Health, Welfare and Sport is the competent authority if the *CCMO* is the reviewing committee; the *CCMO* is the competent authority if the MERC is the reviewing committee. (Article 13i) "The *CCMO* or .... Our Minister will submit substantiated grounds for non-acceptance of a clinical trial if the European database already contains information on adverse reactions to the medicinal product to be tested which pose unacceptable risks to the trial subjects..." (Article 13j)

Table 1 Continued - Overview of the roles and responsibilities of Dutch public supervisory bodies over time

Dutch public supervisory bodies	Roles and responsibilities based on the WMO of 1999	Type of public supervisory body	EUCTD of 2001	Dutch public supervisory bodies	Supplemented roles and responsibilities based on the revised WMO of 2006
Dutch Health Care Inspectorate	"Responsibility for verifying compliance with the provisions laid down by or pursuant to this Act rests with officials of the Public Health Inspectorate designated by decision of Our Minister." (Article 28) The Inspectorate is also responsible for conducting inspections, but does not assess research protocols.			*Competent authority: (3) Dutch Health Care Inspectorate*	"At the request of the *CCMO* or … Our Minister, the Health Inspectorate will verify whether the conduct of a clinical trial involving medicinal products is expected to be in accordance with the present Act." (Article 13j)
Medicines Evaluation Board (MEB)	The MEB assesses and monitors the efficacy, risks, and quality of human medicinal products. (http://english.cbg-meb.nl/about-meb)			*Competent authority: (4) MEB*	The *MEB* collects data on the adverse effects of medication in clinical trials and transmits it to the European Clinical Trials Database (EudraCT). (Article 13m)

The result of the implementation of the EUCTD in Dutch national legislation is an example of what Mahoney and Thelen call layering. Because the legislator had the ability to construct new institutional solutions alongside old ones, it chose the advantages of maintaining its established system over the complexity of adapting to an entirely new one. As a result, new institutions did not replace existing ones, but were added to them, and altered the structure of the original institutions (Thelen, 2003; Thelen, 2004; Streeck & Thelen, 2005; Mahoney & Thelen, 2010). In the next sections, we examine how this layered institutional structure creates a necessity for institutional work and leads to other forms of incremental institutional change.

Institutional drift in public supervision of ongoing trials

This section analyzes the impact of layering on the practice of public supervision of ongoing trials. As mentioned in § 1, the organizational structure of public supervision in the Netherlands is complex and fragmented. This creates two external conditions for institutional drift in ongoing trials: the ambiguity in the allocation of roles and responsibilities between the Dutch Health Care Inspectorate (WMO 2006, Article 13j, Hernandez, 2009) and MRECs, and deficiencies in their abilities to fulfill them. We demonstrate here that the institutional work of actors trying to resolve these difficulties leads to institutional drift.

Prior to the amendment of the WMO, the Ministry of Health, Welfare and Sport released a statement clarifying that the Inspectorate must monitor continued compliance with guidelines throughout the execution of trials[13]. The Inspectorate has the responsibility to conduct inspections, and the power and capability to collect any information necessary from the sponsors of a trial. However, it does not have the power to terminate or suspend a trial if unacceptable risks for subjects are identified. The MRECs do have this formal authority (WMO 2006, Article 3a), but have far less resources to conduct a thorough oversight (see Table 1). The disparity between each body's responsibilities and their ability to fulfill them impairs the efficacy of day-to-

[13] Tweede Kamer der Staten-Generaal. (2005). Evaluatie Wet medisch-wetenschappelijk onderzoek met mensen (WMO). Brief van de staatssecretaris van Volksgezondheid, Welzijn en Sport. Vergaderjaar 2004–2005, kamerstuk 29 963 nr. 2 p. 8-9.

day activities. For example, MRECs receive (serious) adverse event (SAE) reports and notifications from sponsors, and some of these reports contain limited information. It is often impossible for MRECs linked to a University Medical Center (UMC) or teaching hospital, with limited funding and personnel, to fully process all (S)AEs, let alone verify their accuracy.
These results were also found in evaluations of the WMO in 2004 (Dute et al., 2004) and 2012 (Stukart et al., 2012).

> SAEs are really a problem. You cannot judge them accurately, because you do not have the data and the context. And it is so much. The risk is that you might miss something. Actually, an arrangement is needed. We already have been talking to other parties, but decided to let it go, because the new EU Regulation is expected to change the whole system. (interview MREC secretary)

These issues call for continual institutional work by individual actors, and feature prominently in the interviews we conducted. In 2006, the Ministry of Health began holding forums in an attempt to clarify the allocation of roles and responsibilities and facilitate communication between the different supervisory bodies.

> There have been quite a lot of problems. For example, who is responsible for what? It was helpful to have everyone sit down and express their mutual expectations and irritations. It is about a good division of tasks. For example, the CCMO and the Inspectorate: supervision. Well, supervision of what? Try to make a clear line where the responsibility of one ends and that of the other begins. Not only to improve mutual relations but also to improve relations with stakeholders, who sometimes no longer understand who is responsible for what. (interview CCMO employee)

The interviews we held showed that, in practices of studies oversight, everyone is searching for a proper solution. Some respondents suggested that the different supervisory bodies should work more closely in tandem, and that the workload should be more efficiently distributed between them. Others believe that the powers of each supervisory body should be better

aligned to their basic roles, for instance, by giving MRECs more resources to fulfill their current responsibilities. However, these solutions would require legislative intervention to implement, and until the legislation is adjusted, actors must continue to engage in institutional work to resolve the situation.

The ambiguities in the legislation caused by layering have not been properly addressed, partly by actors and partly by the legislators who have not undertaken any action until now. This requires actors to perform institutional work in order to interpret legislation and act accordingly. Our research shows that this institutional work leads to further incremental institutional change. This is the form of institutional change that Mahoney and Thelen term drift, because the disunity between the rules and their enforcement is being neglected. Drift can create a vacuum in the supervisory chain if actors do not take the initiative to define their roles, and further ambiguity surrounding the interpretation and enforcement of legislation if they do. The institutions therefore seemingly remain static, but their impact continually changes according to the institutional work of individual actors. Our examination of ongoing trials in the Netherlands thus creates a clear picture of the dynamic cycle between institutional change and institutional work. In the next section, we expand on this by examining further incremental institutional change in the supervision of international trials.

Institutional conversion in public supervision of international multicenter trials

The international context of multicenter trials is another example of how institutional work creates further incremental institutional change, in this case, conversion. We examine the efforts of the EMA to reduce the disadvantageous effects of possible differences in interpretation of GCP rules across Member States. This allows us to observe institutional work at an EU level, as well as institutional work done by actors at a national level, and how this facilitates conversion.

Enacting both EU-level institutions and multiple Member States' national institutions creates the need for the EMA to engage in institutional work to aid in harmonization. The EMA coordinates inspections held by the Member States' competent authorities (EUCTD, Article 15) and provides secretariat

support to the EU GCP Inspectors Working Group (IWG). The IWG meets on a regular basis to discuss the latest developments in regulations and inspections, as well as the grading of findings on the conduct of clinical trials. It is thus a crucial arena of contention, and its rulings often have an impact on substantive outcomes (Hacker et al., 2013). However, it is challenging to reach a consensus between members of the EMA on the most accurate interpretation of specific rules and the appropriate grades for findings.

> There are some differences in the way findings are graded. That is something that can be challenging: harmonizing how findings are graded across the EU, considering the different cultures and different personalities of inspectors. (interview senior staff member EMA)

However, even as the EMA utilizes its authority to consolidate the interpretation of rules, in practice, conversion cannot be avoided. Because different national authorities are each responsible for supervising the application of GCP rules within their jurisdictions, there will naturally be differences in interpretation of legislation. When the differences become significant enough to diverge from the original intention of the legislation, and the enactment of rules changes, it can be called conversion.

Our observation of four national GCP inspections allowed us to more closely examine the process of this conversion, especially in one of the inspections, which highlighted the cooperation between sponsors and CROs. It showed that interpretations of findings are naturally subject to discussion, which may invite conversion. This is especially prevalent where international multicenter trials are concerned; a national inspectorate has but a limited ability to influence a sponsor or CRO operating in an international context. It can be unclear, for example, how the sponsor or CRO of an international multicenter trial is obligated or able to respond to the findings of a national inspectorate when they are attempting to meet multiple sets of regulations and uphold consistent internal protocols. If various Member States' inspections have different interpretations of institutional rules, international actors cannot satisfy all of them to their fullest extent. This could potentially put the work of a national inspectorate under pressure.

> It is not because of the opinion of the Dutch Health Care Inspectorate that we are suddenly going to update all possible procedures based on a finding for which no correct reference or requirement was indicated. We work not only for the Netherlands, but worldwide and with global procedures, which are in line with ICH GCP and European Directives and also avoid conflicting with local (in this case, Dutch) legislation. (interview CRO employee)

Thus, when actors must attempt to put legislation from multiple authorities into practice, interpretation can diverge significantly enough from the intention of legislation that it becomes conversion. This can be seen both in the implementation of EU legislation in individual Member States and in a multicenter trial setting, and is another example of the dynamic cycle of institutional change and institutional work. The need to comply with layered legislative systems requires institutional work. This leads to significant incremental institutional change in the form of conversion.

Discussion

Our research was initiated to gain more insight into how actors in the field of public supervision of clinical trials attempt to implement the changes wrought by the EUCTD. We studied legislation in detail at different levels and compared it with the findings of our interviews and our observations of Dutch inspections. The research we conducted revealed a disunity between legislation and its functional applications that was caused by layering as a response to harmonization attempts. We observed that efforts to harmonize GCP at an EU level can cause problems in the interpretation and application of GCP rules at a national level.

Several articles and reports posited that the EUCTD's intended harmonization of the international regulatory framework for clinical trials has not been fully achieved (European Commission, 2009; European Forum for Good Clinical Practice, 2009; Hernandez et al., 2009; The Academy of Medical Science, 2011; Gluud et al., 2012). Our research in the Netherlands supports this, and demonstrates multiple reasons for the continued disharmonization. We observed that attempts to integrate the EUCTD with existing national

legislation have produced a complex multilevel legislative framework in the Netherlands. This layered framework creates difficulties in the actual practice of public supervision of ongoing trials. It requires continuous institutional work and institutional change to implement and interpret legislation, which leads to discrepancies in the interpretation of GCP rules. This suggests that attempts at harmonization can become counterproductive when they result in layering. Layering can be partially necessary in order to integrate EU and national institutions, and is a natural attempt to preserve the achievements of existing national institutional structures. However, it also alters the structure of institutions, creating ambiguity that, when left unresolved, requires individual actors to compensate through institutional work. This instigates institutional drift and conversion, which can ultimately lead to significant, widespread discrepancies in the interpretation of EU legislation. Legislation created to harmonize can thus lead to serious institutional differences between Member States, culminating in further attempts at harmonization through the upcoming Regulation.

Nowadays, Member States each have established institutional practices of public supervision, and the EU does not wish to, nor should it, dismantle their existing benefits and expertise. It can be assumed that the implementation of the new Regulation will result in similar layering to that which began with the Directive in the Netherlands. This could set in motion a dynamic cycle of institutional change and institutional work that could easily have detrimental or unintended effects. It is therefore crucial for EU and national legislators to recognize the processes of institutional change. If they better understand where, why, and how harmonization attempts can cause institutional change, they can take steps to engage with the consequences of these changes.

At an EU level, the EMA can provide crucial support in monitoring processes by creating opportunities to discuss and evaluate findings and share effective solutions. However, the authorization and oversight of clinical trials remains the responsibility of Member States (European Medicines Agency, n.d.). The ability to anticipate and adjust to the consequences of implementing the 2018 EU Regulation rests largely on domestic politics and policies. At a national level, we suggest that Member States anticipate, monitor, and adjust to these changes before they can become ingrained, and therefore more difficult to

influence, or cause detrimental repercussions, such as compromising the supervision of ongoing trials. For example, drift can be avoided by clearly establishing the roles and responsibilities of each supervisory body, and granting them access to necessary information and tools accordingly. Conversion can be alleviated by continually observing when it is necessary to adjust legislation to take into account practical application. In order to execute these measures effectively, it is important to seek input from actors undertaking practical application of legislation, and help facilitate communication and coordination between them.

Conclusion

Our analysis shows that the concepts of institutional change and institutional work can be utilized to better understand the consequences of EU-level harmonization policies on national public supervision. Applying these theories to our research allowed us to look beyond the surface legislation to how EU policies are applied in the less visible practices of public supervision.

In our case study, the Netherlands' attempt to implement EU standards for conducting clinical trials animated a dynamic cycle of institutional change (layering), institutional work, and further incremental institutional change (drift and conversion). This indicates that, if not carefully implemented and adjusted to political, economic, scientific, and ethical environments, legislation intended to strengthen harmonization can become counterproductive. Most importantly, the examples of drift and conversion demonstrate that failing to adapt legislation to practical applications can result in an inefficient system of supervision, and a significant divergence from the intended effects of legislation. Ideally, pre-emptive consideration of institutional change and its consequences is essential to both implement EU harmonization policies and maintain a working system of national public supervision.

However, our research shows that institutional change and its consequences are not always easy to detect, because of the fundamental obscurity of these processes. They can sometimes only become clearly visible years after new legislation has come into effect. This is because most of these changes occur

not so much at a legislative level, "the law in books", as at the ground level of the daily execution of legislation, "the law in action" (Pound, 1910). They can only be observed on a larger scale once a pattern emerges and the changes have already been established. It is therefore advisable to study the processes of institutional change in the long-term if we wish to effectively implement harmonization policies. We believe additional field research is needed to analyze institutional change, and in the future, to empirically examine the consequences of the new EU regulation.

Chapter 3

Institutional work in respond to external challenges in public supervision of ongoing clinical trials

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Abstract

Background

National regulatory regimes for supervising ongoing clinical trials are affected by external challenges, both international, such as harmonization of EU legislation, and national, such as critical reviews of incidents. This study examines how supervisory bodies dealing with ongoing trials respond to external challenges of the past two decades and engage in institutional work to maintain, repair, or improve the Dutch regulatory regime.

Methods

International and national regulatory documents were analyzed and interviews (*n*=27) were conducted with various actors, including public supervisory bodies, hospital staff, and boards of directors.

Findings

In the Netherlands, EU harmonization directed at centralizing and coordinating the regulatory regime for good clinical trial practice in Member States has paradoxically led to further fragmentation. The resulting ambiguity and inefficiency remained largely unresolved until a serious incident in a university hospital became a catalyst to clarify both the interconnected responsibilities and working relationships of various supervisory bodies. New legislation and regulatory methods were implemented, and actors outside the legislative framework became active in the field in order to strengthen supervision of ongoing trials, further multiplying yet also aligning with existing regulatory regimes.

Conclusions

Public supervision of ongoing trials is fragmented in the Netherlands because the responsibilities and resources are unevenly distributed. In countries like the Netherlands, public supervisory bodies must do a great deal of institutional work to align with new EU regulations and still safeguard their traditional regulatory mechanisms that protect human safety. However, national regulatory traditions also offer new opportunities to strengthen the quality assurance of clinical trials.

Keywords

Public supervision; Clinical trials; Institutional work; Regulatory regime

Introduction

Clinical trial practice is highly regulated (Keating & Cambrosio, 2012). While it is accepted that some risk is inevitable, regulatory regimes are intended to reduce risk to a minimum (Seiler, 2002). To secure protection of human subjects and data validity and integrity, clinical trial practice is enforced by legislation and the institutionalized practice of supervision, together constituting the regulatory regime. Supervisory bodies must simultaneously change and maintain their regulatory regime in response to challenges such as critical reviews of national legislation or severe incidents.

In recent years, various attempts have been made to harmonize legislation and regulation of ongoing clinical trials within the European Union (EU). EU harmonization creates a massive ongoing challenge for Member States to align international regulation with national law and supervision practices, with various national attempts taking place over time (McMahon et al., 2009). The Netherlands in particular provides an interesting case to analyze the work required to achieve alignment with new EU rules and national regulatory regimes, since the traditional Dutch system differs significantly from the EU framework. Moreover, this country was confronted with a severe incident, the Propatria case, which raised a lot of media coverage. This paper focuses on the supervision of ongoing clinical trials in the Netherlands, as this area is less clearly regulated than the approval phase.

This paper uses an institutional theoretical framework, adopting the framework of Hood, Rothstein, and Baldwin (Hood et al., 2011) to explore how the regulatory regimes of clinical trials work and understand the forces that shape them. The concept of institutional work elucidates the dynamic interplay between actors and institutions (Lawrence & Suddaby, 2006), and focuses on how actors deal with external challenges, how they enact and adapt their everyday regulatory practices, and how they cooperate when reacting to external challenges. It enables us to examine in-depth how developments in EU legislation, and pressure from regulatory reviews and incidents, triggered changes in the Dutch regulatory regime, creating incongruity between legislation and actual practice in the supervision of ongoing trials.

The research question guiding this paper is: How do supervisory bodies in the public supervision of ongoing clinical trials in the Netherlands respond to the external challenges of the past two decades and engage in institutional work to maintain, repair, and improve the Dutch regulatory regime?

We detail how supervisory bodies faced with external pressures undertake institutional work to both change and preserve their institutions. We look at how alignment between the various supervisory bodies comes about, where frictions occur, how these are handled, and what kind of work is needed. In our case study, these challenges, and subsequently their dynamics and frictions, not only call for repair or maintenance work, but also create new space to stimulate action for improvement.

The paper is constructed as follows. The next section focuses on how the risk regulation framework and institutional work theory can help us study change and continuity in the institutional regulation regime of ongoing trials. Section 3 explains the regulatory regime of clinical trials in the Netherlands. Section 4 describes the research methods, while section 5 presents the results. Finally, section 6 presents the discussion, describing the impact of our results on both theory and regulatory practice and ending with conclusions. We believe that the mechanisms the Dutch public supervisory bodies use to deal with external challenges are relevant to other countries and domains, as any national supervisory body has to respond to these challenges within their own traditions.

Theory

A risk regulation regime framework

Hood et al. (2001) define risk regulation regimes as "the complex of institutional geography, rules, practice and animating ideas that are associated with the regulation of a particular risk or hazard". Overall, risk-based regulation aims to set standards, collect information, and influence and change behavior. Risk regulation regimes are based on three features. First, regimes are seen as systems, as sets of related, interacting parts. They are interested in both the activities of front-line people and the standard-setters and policy-makers at the center of government, as well as the relationship, if

any, between the two. Second, regulation regimes have some degree of continuity over time. Third, because of the system-based approach, regimes are conceived as "relatively bounded systems that can be specified at different levels of breadth" (Hood et al., 2001). Consequently, it is important to specify carefully which level of regime is being analyzed and the kind of risk the regime addresses.

Institutional work

The concept of a regulatory regime stresses that "institutions matter" (Windholz, 2018). Institutions are commonly defined as systems of prevalent, established rules that structure social interactions (Hodgson, 2006). They provide a degree of stability and have an important regulatory function in society (Beunen & Patterson, 2016). This does not mean that institutions cannot change. This article uses the concept of institutional work to consider both stability and change. This concept can help analyze how regulatory actors not only respond passively to external challenges but also actively engage in three types of institutional work: the creation, maintenance, and disruption of institutions (Lawrence & Suddaby, 2006; Bochove & Oldenhof, 2018). Creation work involves establishing rules and constructing rewards and sanctions that enforce these rules. Maintenance work entails supporting, repairing, and recreating social mechanisms that ensure compliance with existing institutional norms. It seeks to ensure conformance with rules and systems and reproduce prevailing norms and belief systems. Disruption work involves attacking or undermining the mechanisms that lead actors to comply with institutions (Lawrence & Suddaby, 2006). Institutional work theory thus draws attention to a relatively overlooked subject in mainstream institutional theory: the lived experiences of organizational actors (Lawrence et al., 2011 and 2012). It suggests studying actions in a day-to-day setting to focus on local, creative, incremental practices and processes rather than on outcomes to gain an understanding of how institutions evolve.

The notion of institutional work is of particular interest to our investigation of the public supervision of clinical trials in the Netherlands for three reasons. First, it recognizes public supervisory bodies as embedded agents who are not merely executors of regulation, but whose activities contribute to shaping institutional regulatory regimes. Second, implied in the notion of institutional

work is the idea of effort in the face of resistance or challenge. Institutional work is considered true "work," as it involves challenging and negotiating existing rules, practices, and beliefs that may be in opposition (Wallenburg et al., 2016). Third, it recognizes the distributed, pluralistic nature of change in the regulatory regime, where regulatory bodies interact with a wide spectrum of actors, none of whom have complete control or oversight, hence underscoring the aspect of ongoing regulatory uncertainty (Mills & Koliba, 2015). While one public supervisory body may strive to disrupt institutional arrangements and create new ones, others may strive to maintain those that appear to favor them. Hence, the theory of institutional work allows us to observe the immediate effects of new regulations and incidents and the mundane practices of institutional repair and maintenance work that they set in motion.

EU harmonization attempts, incidents, and other triggers may reveal a misfit between legal regulation and the daily practice of supervision of ongoing trials. Actors manage, exploit, and adjust their actions to the ambiguity, pluralism, and contradiction in regulatory regimes (Cloutier et al., 2016).

In this study, we seek to explore the institutional work of three Dutch public supervisory bodies in the regulatory regime of ongoing trials, tracing the effects of external challenges on their working methods and relationships. Before turning to our findings, we will first explain the institutional regulatory regime of clinical trials in the Netherlands.

The regulatory regime of clinical trials in the Netherlands

The Netherlands has a decentralized structure of supervision, introduced in 1999 with the Medical Research Involving Human Subjects Act (WMO)[14] (CCMO, 2009a). It stipulates the conditions permitting clinical research involving human subjects in the Netherlands and established a new supervisory body: the Central Committee on Research Involving Human Subjects (CCMO). Unlike other countries in the EU, in the Netherlands the

[14] Staatsblad van het Koninkrijk der Nederlanden. (1998, 161). Wet van 26 februari 1998, houdende regelen inzake medisch-wetenschappelijk onderzoek met mensen (Wet medisch-wetenschappelijk onderzoek met mensen) [Medical Research involving Human Subjects].

assessment of research protocols is based on the historically institutionalized notion that science and ethics cannot be viewed separately; these two aspects come together in an integrated assessment procedure carried out by local medical research ethics committees (MRECs). This perspective, however, conflicts with the EU vision that the two aspects must be reviewed by separate bodies (Van Oijen et al., 2017).

The WMO stipulates that a sponsor of a clinical trial with human subjects may not start the trial until an MREC has approved the research protocols. Most MRECs are linked to a university medical center (UMC) or one or more general hospitals, and a few work independently. MRECs are accredited and supervised by the CCMO, which can create new guidelines, for instance with regards to the required expertise of MREC members. Research proposals and their MREC assessments must be registered with the CCMO. The Health and Youth Care Inspectorate (IGJ), in turn, is responsible for verifying compliance with the WMO (1999, Article 28) and for conducting inspections of clinical trials.

In 2004, the EU Clinical Trials Directive 2001/20/EC (EUCTD)[15] was introduced. The EUCTD aims to harmonize rules for clinical trials conducted across EU Member States. In the EU framework, supervision of clinical trials is the responsibility of Member States. Each Member State has sought alignment with the EUCTD based on their existing systems and traditions. The Dutch procedure of decentralized supervision deviates from the centralized, separated assessment procedure that the EUCTD advocates, which is more in line with other EU countries' regulatory systems, such as that of the UK.

The Dutch government decided to implement the EUCTD by modifying the WMO (2006)[16]. It created a special section for clinical trials that meets the

[15] European Parliament and of Council of the European Union. (2001). Directive 2001/20/EC of the European Parliament and the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. Official Journal of the European Communities, L121(May), 34–44.

[16] Staatsblad van het Koninkrijk der Nederlanden. (2006, 644). Wet van 30 november 2006 tot wijziging van diverse wetten op of in verband met het terrein van VWS, ten einde wetstechnische gebreken te herstellen en andere wijzigingen van ondergeschikte aard aan te brengen (Reparatiewet VWS 2006).

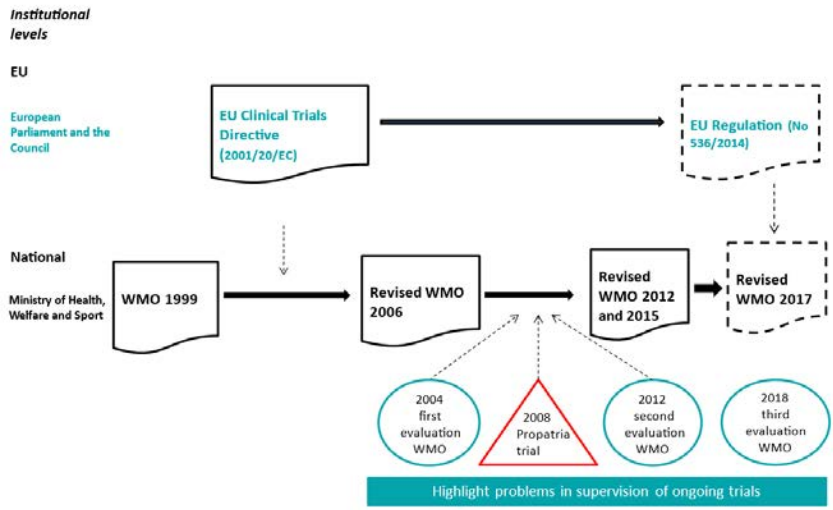
requirements of the EUCTD (WMO 2006, Article 13). The EUCTD requires a clinical trial to be approved separately by a competent authority assessing the medical and scientific aspects of a protocol and an ethics committee verifying the primary ethical concerns (EUCTD, Article 2). The Dutch government installed a dual review process, which continues the established integrated assessment of protocols by MRECs and adds a marginal role for the CCMO to act as competent authority. Following this procedure, in cases where the CCMO acts as the reviewing committee, the Ministry of Health, Welfare and Sport is the competent authority (WMO 2006, Article 13-i and -j). In a more general sense, the IGJ also fulfills the role of competent authority. This set-up is quite different in other European countries that have only one competent authority, such as the Medicines and Healthcare products Regulatory Agency, the authority responsible for clinical trial approval, oversight, and inspections in the UK. Whereas the UK has one supervisory body for ongoing trials, the Dutch have these three main bodies, resulting in a fragmented regulatory regime (Van Oijen et al., 2017) (see Table 1 for an overview of the responsibilities of the Dutch public supervisory bodies the IGJ, CCMO, and MRECs; see Figure 1 for the historical development of the regulatory regime).

Table 1 Responsibilities of Dutch supervisory bodies laid down in the WMO in 1999 and 2006 after implementing the EUCTD

Super-visory body	Level	Responsibility	WMO 1999	Added responsibility	WMO 2006
IGJ	Centra-lized	Verifying compliance with the provisions laid down by the WMO and conducting inspections of clinical trials	Article 28	At the request of the CCMO or Ministry of Health, verifying whether a clinical trial involving medicinal products is in accordance with current WMO	Article 13j
CCMO	Centra-lized	Regulating the accreditation of MRECs and overseeing their operations	Articles 16 and 24	Acting as competent authority if an MREC is the reviewing committee	Article 13i
MRECs*	Decen-tralized	Assessing and approving research protocols	Article 2	Receiving safety reports of ongoing trials involving medicinal products	Article 13o and 13p

*Important note: MRECs conduct many of the responsibilities of a competent authority, but are not regarded as a competent authority themselves.

Figure 1 The regulatory regime in the Netherlands and the impetus to focus on supervision of ongoing trials



Since 2000, the Dutch regulatory regime for assessing clinical trials has met several challenges. Reviews of national legislation and supervisory practices have exposed several weaknesses in the regulatory regime. The first evaluation of the WMO in 2004, prior to the introduction of the EUCTD, highlighted the unclear division of tasks between the IGJ and CCMO (Dute et al., 2004). The second evaluation in 2012 revealed that responsibilities regarding the handling of serious adverse events (SAEs) were unclear (Stukart et al., 2012). The third evaluation in 2018 showed issues created by the complicated working relationships among the IGJ, CCMO, and MRECs (Ploem et al., 2018). Overall, the evaluation reports noted bottlenecks in the regulatory regime and task division between public supervisory bodies in the supervision of ongoing trials.

Besides EU harmonization and critical reviews of regulation, the Dutch regime is affected by incidents that attract public attention and act as catalysts (Bozeman & Anderson, 2016), such as the Propatria trial in 2008, which was widely covered by the Dutch media. This investigator-initiated trial (IIT), a probiotic study of acute pancreatitis, was conducted in fifteen hospitals. As the sponsor, the UMC leading the study took responsibility for the initiation,

management, and financing (EUCTD, Article 2). Twenty-four patients in the probiotic group died of their disease, compared to nine patients in the placebo group (see Figure 1 for place in timeline).

The subsequent investigation conducted by the IGJ and CCMO, among others, highlighted several serious shortcomings in the design and execution of the research protocol, the information on side effects provided to the patients, and the reporting of SAEs—only two of the 33 deaths were reported immediately (IGJ et al., 2009; Zaat & De Leeuw, 2009; science.org, 2009). Furthermore, the Propatria report revealed that the hospital's board of directors failed to meet its responsibilities as sponsor in terms of the WMO. The safety of human subjects had been inadequately secured because several actors had not ensured that clear and efficient reporting procedures were in place (IGJ et al., 2009). The recommendations of the Propatria report thus fostered a focus on the roles and responsibilities of the MRECs as a supervisory body, and on the boards of hospitals as a sponsor. We expand on this in the results section, but first let us discuss our methods.

Methods

Research design

To gain insight into how and why changes in the regulatory regime of ongoing trials do or do not occur due to external challenges and how Dutch public supervisory bodies undertake institutional work to engage with these challenges and preserve their institutions, we conducted an exploratory qualitative study. First, to understand the chronology of changes to the regulation of clinical trials and the responses of public supervisory bodies, we studied documents on the Dutch situation, such as legal documents, annual reports of supervisory bodies, and previous research on the development of regulation regarding clinical trials (see Table 2 in Appendix A). The starting point of this document study was 1999, the year the WMO was launched and

the CCMO was established. We use 2018 as the end point, as the consequences of the next round of harmonization, the European Clinical Trials Regulation No 536/2014 (ECTR)[17], became apparent then and the third evaluation of the WMO was published.

Second, we conducted semi-structured interviews to study the institutional work of actors involved in the public supervision of clinical trials. We interviewed inspectors from the IGJ (*n* = 9; one inspector three times); employees of the CCMO (*n* = 3; one employee twice) and the MRECs (*n* = 5); as well as the board and staff of hospitals (*n* = 10; one staff member twice). Interviews focused on working methods and mutual relationships (see topic lists in Appendix A) and took place between December 2013 and May 2018. With the permission of all respondents, the interviews were audio-recorded and transcribed in full. The interviews lasted between 40 and 90 minutes. The processed interview data were submitted to the respondents for member check. In the Netherlands this research requires no ethical approval.

Data analysis

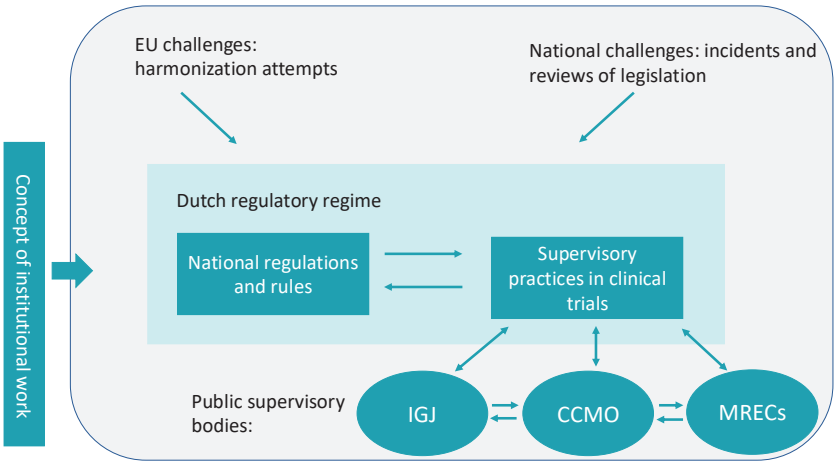
Triangulating the results of the document analysis and the interviews enables us to develop an understanding of the external challenges Dutch public supervisory bodies faced in the past two decades and the kind of institutional work this required (see Figure 2).

When new issues emerged in interviews or in the news, we searched further for relevant documents, moving iteratively between our data (desk research and interviews) and the literature on risk regulation regimes and institutional work.

During data collection, we met regularly to analyze the data. Using inductive and deductive coding, based on regulatory regime and institutional work frameworks, we looked for relevant themes and the labels (codes) to index them.

[17] European Parliament and of the Council of the European Union. (2014). Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive /20/EC. Official Journal of the European Union, L158(May), 1–76.

Figure 2 Overall scheme of the research focus



As forms of institutional work emerged, we debated the themes and codes until we reached a consensus. We identified three overarching themes that represented the supervisory bodies' responses to external challenges since 2000: (1) clarifying the division of roles and responsibilities in the supervision of ongoing trials, (2) dealing with the daily control of safety reports by MRECs, and (3) developing IIT inspections of hospitals as trial sites by the IGJ (see Table 3 in Appendix A).

Results

Legal evolvement, critical evaluations, and the Propatria trial highlighted weaknesses in the supervision of ongoing trials. We analyzed how these challenges not only became effective catalysts for transforming processes in supervision, but also induced repair work to maintain the regulatory regime. This section shows how supervisory bodies such as the IGJ and CCMO do long-term institutional work, focusing on how they operate and endeavor to strengthen their own position (§ 5.1), and the position of other actors such as MRECs (§ 5.2) and hospital boards of directors (§ 5.3).

Clarifying the division of roles and responsibilities in the supervision of ongoing trials

The national legislator's division of roles and responsibilities has influenced the relationship between the CCMO and IGJ. As pointed out above, the supervisory roles of both bodies have somewhat overlapped since the launch of the WMO in 1999 (Aartsen, 1999). The WMO states that the IGJ must supervise the full scope of the WMO, which implies that it also supervises the entire system set for clinical trials subject to the WMO, including other supervisory bodies, which is a quite sensitive task:

> Strictly, I think we [the IGJ] supervise it all, including the CCMO and the MRECs […]. But yes, no one likes that, so no one would ever admit it. (interview inspector 1 IGJ, 2014)

Discussion of each other's jurisdiction flared up in 2003, when the IGJ took the initiative to inspect several MRECs and the CCMO:

> It's true, in the past we sometimes had differences of opinion with the IGJ: who supervises whom? And eventually, in 2003, the IGJ supervised MRECs, including us. But that didn't feel good, frankly. [...] There's a lot open to interpretation: where does it [division of authority] begin and where does it end? (interview employee 1 CCMO, 2014)

Researchers involved in the first evaluation of the WMO in 2004 also observed this tension between the CCMO and IGJ (Dute et al., 2004). The evaluation recommended focusing more on supervising ongoing trials and insisted on clarifying the responsibilities. In 2005, the Ministry of Health released a white paper that redefined the roles and responsibilities of the IGJ and the CCMO (see Table 2) to repair the regulatory regime. This form of maintenance work ensures compliance with existing regulation.

Table 2 Division of tasks between the IGJ and the CCMO[18]

Division of tasks	Supervisory body	Explained in more detail
1. Supervision aimed at quality improvement and harmonization of accredited MRECs	CCMO	§ 3 and § 5.2
2. Supervision of the CCMO: assessing whether the CCMO complies with the law	IGJ	§ 5.1
3. Supervision of compliance in practice (e.g. that the research is carried out according to the protocol, permission procedures have been adequately carried out, and there is an insurance policy)	IGJ	§ 5.2
4. Supervision as a result of an incident in ongoing research (e.g. the Propatria trial)	IGJ in cooperation with CCMO	§ 5.1-5.3

The IGJ received the explicit responsibility to supervise the CCMO. However, when we focus on this supervision, we see that this never really worked (Ploem et al., 2018). Beyond the aforementioned action taken in 2003, in practice the IGJ does not monitor the actions of the CCMO, allegedly because there has been no direct reason for the IGJ to take specific supervisory action in terms of monitoring risks or incidents.

After the Ministry allocated the roles and responsibilities, the IGJ and CMMO still needed to interpret their tasks. The IGJ's supervisory role means that if the results of an inspection necessitate a review of the MREC, the results are first passed to the CCMO. Therefore, the IGJ and CCMO need to communicate frequently to keep each other informed. At first, the communication was informal and less structured. After the WMO was introduced, however, they did not automatically exchange information. Based on its legal task, the CCMO manages a national registration system which records all ongoing studies assessed in the Netherlands. The IGJ has no access to this database, so if they want information on a particular study, they have to submit a request to the CCMO. In this relatively stable stage, the institutional work was

[18] Tweede Kamer der Staten-Generaal. (2005). Evaluatie Wet medisch-wetenschappelijk onderzoek met mensen (WMO). Brief van de staatssecretaris van Volksgezondheid, Welzijn en Sport. Vergaderjaar 2004–2005, kamerstuk 29 963 nr. 2 p. 8-9.

aimed at maintaining the regulatory regime, organizing ad hoc information exchange so that both bodies could preserve their own roles and responsibilities.

The Propatria trial was a window of opportunity to discuss the relationship between the IGJ and CCMO because it forced both authorities to work together more closely. For the first time, the two investigated an incident together (see point 4 in Table 2). This led to a joint final report, together with the Netherlands Food and Consumer Product Safety Authority (IGJ et al., 2009). One CCMO employee recalls:

> Over the years, we've realized that we just have to cooperate. The Propatria trial was the first time we really worked together on investigating an incident. It really instigated the cooperation with the IGJ, and everyone played their own part. It actually went very well, and so did the drafting of our joint report, which was based on the three separate reports from each authority. (interview employee 2 CCMO, 2018)

Subsequently, the IGJ and CCMO performed coordination work, as a form of creation work, organizing informal and formal consultations on both administrative and official levels. The purpose of the formal consultations is to discuss the practical implementation of matters that cover their legal tasks and responsibilities. For example, they agreed that the IGJ will inform the CCMO if it intends to visit an MREC during an inspection of an ongoing trial. The chosen division of tasks in the regulatory regime hence requires investment in cooperation between the CCMO and IGJ to ensure task coordination and the management of information (CCMO, 2009a). This prompted the IGJ and CCMO to participate together in several EU groups working on the implementation of the ECTR (CCMO, 2009b; IGJ, 2017). In May 2018, they signed a protocol[19] listing agreements on their mutual exchange

[19] Staatscourant. (2018). Samenwerkingsprotocol tussen de Centrale Commissie Mensgebonden Onderzoek en de Inspectie Gezondheidszorg en Jeugd [Cooperation protocol between the Central Committee on Research Involving Human Subjects and the Health and Youth Care Inspectorate], nr. 37731, 9 juli.

of information and coordination. This protocol can be seen as a form of maintenance work. It did not change the legal tasks and responsibilities of either organization, but was intended to prevent overlap or gaps in the supervision of ongoing clinical trials and in the enforcement of laws and regulations.

In short, although their roles and responsibilities were laid down in the WMO and later clarified in a white paper, they were not immediately taken over by the supervisory bodies. In practice, the lack of clarity caused tension, and information exchange was cumbersome. In terms of institutional work, coordination work done by the IGJ and CCMO was essential to respond to external challenges. The Propatria case created a policy window for them to organize their interconnected roles and responsibilities, which refined and strengthened their working relationship.

Dealing with the daily control of safety reports by MRECs

The white paper of 2005 and the Propatria incident, however, did not altogether resolve the ambiguity surrounding the allocation of roles and responsibilities. The IGJ is responsible for conducting inspections of ongoing trials (see point 3 in Table 2). It does not assess research protocols beforehand, which is the task of MRECs, but depends on information provided by sponsors, researchers, and other competent authorities or supervisory bodies, such as annual safety reports, SAE reports, and notifications of unexpected but suspected adverse reactions. This information is primarily assessed by the MRECs, in line with the procedural requirements of the EUCTD.

How did the IGJ and MRECs attempt to compensate for the ambiguity surrounding their roles and tasks? To answer this question, we specifically look at the information flow and how the supervisory bodies process and assess the information received.

Legally, the MREC is tasked with assessing reported SAEs and other sponsor notifications from the standpoint of protecting human subjects[20]. However,

[20] Tweede Kamer der Staten-Generaal. (2015). Wijziging van de Wet medisch-wetenschappelijk onderzoek met mensen in verband met een uitbreiding van de meldingsplicht van ernstige ongewenste voorvallen. Brief van de staatssecretaris van Volksgezondheid, Welzijn en Sport.

we observed major differences between MRECs in the extent to which they are capable of meeting their obligations as stated in the WMO, resulting in major practice variation. Independent MRECs review many proposals for phase I and phase II studies, usually from contract research institutes and pharmaceutical companies that have more funding and pay for the MRECs' legal services. One independent MREC, with enough capacity and resources, closely follows and assesses safety reports, and even investigates the trial site to verify regulatory compliance, even if the legal status of its site report is doubtful:

> We [independent MREC] visit trial sites ourselves at least once a year. [We] do a visitation as an MREC, to see if facilities and procedures are well organized. We pull out one of the ongoing studies at random, visit [it] and talk to one or more [of the] subjects. "What have you been told about this trial?" So, we act like an inspectorate. The status of our report is sometimes an opinion, sometimes a requirement. (interview chairman 1 MREC, 2014)

In contrast, hospital-based MRECs have limited funding and capacity, because they traditionally offer free services to trials executed in their "own" hospital, and capacity does not increase automatically with the increase in trials and submitted documents. These MRECs often find it impossible to fully process all safety reports and notifications, let alone verify their accuracy:

> The detail level has gone up so much that it's a huge workload. Normally, I have this pile on Sundays [indicates stack of papers]. Now it can't come through the mail. Just compact discs. Yeah, it's really hopeless.
>
> You must take care you still pick out the essentials. (interview member of the CCMO and pharmacist-researcher at a top clinical teaching hospital, 2014)

Vergaderjaar 2014–2015, kamerstuk 33 646, nr. 10 p. 2.

> Every week I get this extremely comprehensive set of SAEs where the researcher says that the SAE won't hinder the progress of the study. I believe them and [just] sign the papers blindly. It's correct, administratively. (interview chairman 2 MREC, 2014)

These quotes demonstrate the painstaking work involved in overseeing ongoing trials, but also reveal a lack of supervision by hospital-based MRECs. Our observations are in line with the second WMO review, which states that over half of MRECs found that supervision of ongoing trials was part of their task, but they usually did not have the workforce or financial means to execute it properly (Stukart et al., 2012). Consequently, a lapse in the supervision may occur when a sponsor reports an SAE to an MREC that cannot perform a substantive assessment. This can lead the sponsor to incorrectly conclude that the SAE is not a problem, or that a reassessment of the protocol is unneeded because the MREC has not undertaken any action.

One recommendation in the Propatria report was to report all SAEs in medical research with humans to the specific MREC responsible [24], which is already required for clinical trials with medicinal products (see Table 1). This recommendation prompted the legislator to repair the regulatory regime by mandating improvements to SAE reporting in the revised WMO of 2015, such as timely notification and ensuring that all relevant information about fatal or life-threatening SAEs is reported to the reviewing committee. Recurrently, the legislator did maintenance work to ensure compliance with the regulation. Additionally, the CCMO was legally obliged to report annually on the number of SAEs occurring in the preceding year. Previously, the CCMO had put great effort into gaining insight into SAEs and digitizing SAE reports. This creation work included reconstructing rules, property rights, and boundaries to gain access to SAE reports. Their new obligation gave insight into the amount of work MREC assessments of SAEs involved; 5808 (CCMO, 2017) and 6103 (CCMO, 2018) SAEs were reported in 2016 and 2017, respectively. Almost 5% of these SAEs had serious consequences for human subjects, leading to the termination or suspension of a trial (CCMO 2017 and 2018).

In sum, MRECs deal differently with supervising ongoing trials due to funding, with MRECs in the not-for-profit sector having fewer resources available than those in the profit sector (e.g. pharmaceutical companies). This affects their ability to increase capacity when the workload grows. Over the years, the CCMO's creation work, done to gain a better grasp of SAE practice in ongoing trials, has led to a new legal responsibility for reporting annual numbers of SAEs. Despite all efforts, the division of tasks between the IGJ and MRECs is still unclear. The third WMO review suggests a new round of institutional work, involving the CCMO and hospital boards, to strengthen the position of the hospital-based MRECs in the regulatory regime (Ploem et al., 2018).

Developing IIT inspections of hospitals by the IGJ

The IGJ supervises the execution of all clinical trials in the Netherlands. To respond to and anticipate the results of the Propatria trial investigation, they began to focus increasingly on IITs.

The IGJ selected IITs as a theme to underscore the role and responsibility of hospital boards as sponsors of trials initiated by their organization. We observed major differences in the IGJ's working methods between the first and second round of inspections. In the first round, between 2014 and 2016, they carried out inspections targeting IITs of medical products at seven UMCs and two teaching hospitals. An inspector reflects on why IITs became the new focus:

> We've been saying for years that in some studies it's not so clear that the sponsor [hospital] feels responsible; they should be, but are they really? And that's why the focus shifted to IITs. (interview inspector 2 IGJ, 2016)

A risk model for clinical trials of medical products was developed to make the sponsor's responsibilities transparent and place the hospital's board of directors into the position of sponsor. The legal framework was based on the International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice (ICH GCP) guideline (1996), alongside the WMO. These two elements formed the basis for a detailed assessment of the hospital's practices. A four-day

inspection of a pre-selected study examined the hospital's systems for the organization and execution of clinical trials. The IGJ shared the inspection results at various conferences. Here an inspector reflects on the hospital boards' attitude to their responsibility as sponsor:

> So then you see the [hospital] boards generally do feel responsible, but the extent to which they ensure that a [quality] system gets implemented, well, that fluctuates. (interview inspector 2 IGJ, 2016)

The first round of results showed that general teaching hospitals were often involved in multicenter IITs. In 2016, the IGJ started a second round of inspections of IITs in teaching hospitals, anticipating that the level of quality assurance would differ because research is not a core business of teaching hospitals. Hence, the IGJ created a new database ranking hospitals by their number of studies and the table of contents of their quality assurance manuals. Using these criteria, ten teaching hospitals were selected for one-day inspections in 2016. The IGJ's creation work was to develop a new working method to obtain insight into actual safety practices while keeping the workload "doable". This method permitted quick scans of ongoing IITs rather than in-depth analysis of one IIT (Grit & Van Oijen, 2015). Each hospital was informed of the IGJ's focus on IITs and which departments they would visit. On the day of inspection the IGJ announced which IITs they wanted to review.

> Okay, so we had to find a format to do it in fewer days—but that also means looking in less detail. It can't be otherwise. […] It's new, it's actually the first time that we're not just looking at clinical trials of medicinal products in our proactive supervision […] because […] supervising the WMO implementation doesn't just stop at clinical trials with medicinal products. Because of the ICH GCP, and the tools you have when you look at a study, most of the effort went into clinical trials, but that's different now too. (interview inspector 2 IGJ, 2016)

As the IGJ was no longer inspecting only clinical trials of medical products, the international ICH GCP became unusable. The IGJ sought new legislation which kept the focus on the responsibilities of the hospital boards. The Dutch Healthcare Quality, Complaints and Disputes Act of 2016[21], developed for healthcare in general, formed the basis for its inspections. The IGJ's creation work incorporated altering the boundaries of regulatory systems and interweaving two regulatory regimes; hospital boards are now responsible for having a quality system available for clinical trials.

It is important to note that two of the teaching hospitals involved in the first round of inspections shared their critical findings and experiences with other teaching hospitals through the Association of Top Clinical Teaching Hospitals (STZ), an association of 26 teaching hospitals. This created a sense of urgency among other teaching hospitals, and prompted the STZ to undertake further supportive action. A staff member of one of these teaching hospitals explains:

> Based on our inspection experience, we drew up a document called "Lessons learned". We first discussed this document internally and then with the STZ. It created a flywheel effect and, for example, led to adjustments to 33 STZ standard operating procedures. I think sharing is one of the strengths of the STZ. (interview staff member teaching hospital, 2014)

The STZ's creation work focused on examining "best practices" in top clinical teaching hospitals to create standard operating procedures, which hospitals can use to supplement their quality assurance manuals. This led to an upgraded level of quality assurance. The IGJ was pleasantly surprised to see this learning curve:

> So, actually, it's nice because these hospitals had three years to pick it up. And of course it's also because the teaching hospitals were so open with the other teaching hospitals about what they'd gone through [in the first round

[21] Staatsblad van het Koninkrijk der Nederlanden. (2015, 407). Wet van 7 oktober 2015, houdende regels ter bevordering van de kwaliteit van zorg en de behandeling van klachten en geschillen in de zorg (Wet kwaliteit, klachten en geschillen zorg).

> of inspections after the Propatria case] and what they'd learned from the inspections and to share that with the others. That's where it starts naturally. (interview inspector 2 IGJ, 2016)

The IGJ halted their inspections after visiting eight of the planned ten teaching hospitals, because the same results and recommendations were evident in every hospital. This was made possible because, on the basis of the perceived sharing culture in the STZ, regarded as a serious partner in research, the IGJ presumed that the inspected hospitals would share their results with one another.

The inspectors shared their methods and the results of the inspections with the STZ at various meetings. This quote reveals the boards of directors' growing awareness, especially in teaching hospitals, of their tasks as sponsors of IITs:

> It was so nice […], you really saw the penny drop. That someone said: "So, as a member of the board of directors, I'm responsible for monitoring the multicenter research that we do in other hospitals?" […] "Yes, that's right. And how you organize that—you can talk about that. You're responsible for it." (interview inspector 2 IGJ, 2017)

This came about through the IGJ's institutional work and by including the STZ in their fieldwork.

To sum up, the focus of the IGJ inspections shifted to IITs because of the Propatria trial. This shift involved positioning work by the IGJ, as a form of creation work. Subsequently, they created a context in which "new" actors outside of the public supervisory bodies, the hospital boards, were mobilized to take up their self-regulatory role (Van Erp et al., 2018). The IGJ adopted a framework from a domain outside clinical trials that had to do with regulation of quality of care. Recasting the regulatory regime for hospitals was further stimulated by the Propatria case, underscoring teaching hospitals' interest in

the quality assurance of research. Consequently, teaching hospitals could present themselves as research actors, something that used to be a privilege of UMCs.

Discussion

The purpose of this paper is to examine how supervisory bodies in the public supervision of ongoing trials in the Netherlands respond to external challenges, and engage in institutional work to maintain, repair, and improve the regulatory regime for the safety of clinical trials. The paper shows that changes in (inter)national law and severe incidents in research practice created a window of opportunity for institutional work to both change and protect the regulatory regime. Our findings demonstrate that institutional work is a continuous endeavor at the level of regulatory regimes. Ambiguity sometimes complicated finding the right terms for institutional work. When done by a public supervisory body, institutional work can be considered creation work, changing the regulatory regime, but at the same time it can be regarded as protecting the existing regime. These become interconnected as public supervisory bodies respond to the threats to their status quo and the challenges that create new opportunities. In fact, public supervisory bodies must constantly adapt to external challenges in order to stay the same.

Paradoxically, this research shows that the EU policy of harmonization led to even more fragmentation in the Dutch regulatory regime. Implementing the EUCTD left the decentralized supervision structure in place, whereas the EUCTD stipulated a centralized system. In practice, the IGJ, CCMO, and MRECs needed clarity on who was responsible and accountable for what in the public supervision of ongoing trials. The Propatria trial became a catalyst for the IGJ and CCMO to perform institutional work and act more constructively, and it let teaching hospitals present themselves as research institutes. However, it left unclarities in place, such as the division of tasks between the IGJ and MRECs, especially in the supervision of ongoing research. The layered regulatory regime implies that public supervisory bodies also monitor the public tasks of other supervisory bodies: the CCMO supervises MRECs, while the IGJ supervises all the involved parties. However, between the IGJ and CCMO, the role of "supervising supervision" still needs clarification.

Nowadays, the IGJ is advised to maintain a position such that it can supervise the CCMO (Ploem et al., 2018). In terms of institutional work, these examples show that not all issues can be resolved by public supervisory bodies, due to their historically rooted dominance and interests and the fact that these issues lie beyond their primary roles and capacities.

Overall, institutional theory offers conceptual tools for analyzing the work needed to make regulatory regimes productive. In countries like the Netherlands, with a different tradition from the EU regulatory framework, public supervisory bodies must carry out a great deal of institutional work to align with EU regulations. By focusing on the dynamic interplay between three supervisory bodies in the past two decades, this study contributes to the literature on the relational features of institutional work in two ways. First, our findings demonstrate that institutional work is needed at the level of the regulatory regime because the interplay between evolving regulations and external challenges creates certain dynamics and frictions. Public supervisory bodies continuously need to align with these dynamics while safeguarding existing effective regulatory mechanisms. Second, our findings reveal how public supervisory bodies deal with the external challenges presented by EU harmonization attempts and exposed weaknesses in the regulatory regime. The weaknesses highlighted in the supervision of ongoing IITs, reflected by one adverse incident, became an especially effective catalyst for maintaining and repairing the regulatory regime of the public supervision of ongoing trials. Although other forms of institutional work could be referenced, as the literature has discerned many categories and labels, the institutional work referred to in our case study dealt particularly with coordination work leading to improvements in information sharing, and positioning work to repair and maintain existing institutions. Our case study showed the importance of positioning work, meaning the mobilization and positioning of actors to assume specific roles or do new things, such as bringing actors from outside the legislative framework, in this case hospital boards and the STZ, onto the playing field. This creates new opportunities to strengthen the quality assurance of clinical trials in hospitals.

One limitation of our study is that it is based on a single case in the Netherlands. However, investigating mechanisms like institutional work

requires very detailed data collection to link theory to empirical work (Lawrence & Suddaby, 2006). Triangulation is used as leverage and, in our case study, involves data collected from different places, sources, times, and levels of analysis, and by different methods, such as interviewing stakeholders, analyzing documents, and composing historical descriptions (Brady & Collier, 2010). Particularly, we were interested in the underlying mechanisms that allow regulatory regimes to adapt, given external and internal challenges. By sharing our research findings with several colleagues, from different fields of expertise, we tried to draw valid inferences. Overall, the depth of our study came at the expense of its width.

In conclusion, external challenges like attempts at EU harmonization can be complicated when Member States have divergent regulatory regimes. Harmonization requires more than "just implementing new rules." It requires institutional work by Member States to align existing regulatory regimes with new rules and balance between institutional change and preservation. Given the rise of increasingly international, multi-sited research, such work remains important to safeguard patient safety and data integrity. Zooming in on the supervision of trials in the Netherlands, we observed how EU harmonization attempts created tension in the Dutch regulatory regime and supervision practices. Institutional work is needed to resolve this tension, but new problems may arise from the solutions.

While our longitudinal study focused on the consequences of the EUCTD in the regulatory regime, Member States have prepared to implement the next round of harmonization, the ECTR, which will change the process for starting clinical trials in Europe yet again in 2020 (Tenti et al., 2018) and replace the EUCTD and the national legislation created to implement it (European Commission, n.d.). As a result, the Netherlands has modified the WMO (2017) to meet ECTR requirements and the CCMO has established a National Clinical Trial Office to offer administrative support to MRECs involved in the assessment of multinational studies in the Netherlands (Ministerie van Volksgezondheid, Welzijn en Sport et al., 2018). No end to institutional work is to be expected, given the ongoing adjustments to the existing regulatory regime needed to meet new EU requirements. This paper lays the conceptual and empirical groundwork for studying this kind of work.

Chapter 4

Working on ensuring data quality of investigator-initiated trials in hospitals

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Abstract

The complexity of regulations governing investigator-initiated trials (IITs) places a great burden on hospitals. Consequently, many hospitals seek to alleviate regulatory pressures by seeking an alternative quality management system (QMS). This paper takes the Netherlands as a case. To investigate how QMSs for IITs are organized in Dutch hospitals, we adopted the theoretical concepts of mentoring and monitoring in a mixed methods study in the period 2014–2018. In clinical practice and international guidelines, monitoring is seen as the standard quality assurance for ongoing trials. However, hospitals have implemented monitoring programs that resemble mentoring. The contrast between these ideal types is less pronounced in practice as both combine elements of compliance and feedback for learning in practice. In a monitoring setting, learning is one-way, from monitor to researcher; whereas mentoring focuses on mutual support and learning. To tackle problems in each system, the authority of the Board of Directors (BoD) and the BoD's relationship with staff members are crucial. We discuss the challenges that BoD and staff face in keeping an integrated view of the various components of QMSs.

Keywords
Mentoring; Monitoring; Quality Management System; Investigator-initiated trials; Data management

Introduction

Investigator-initiated trials (IITs) significantly contribute to medical knowledge (Shafiq et al., 2009) and have an important bearing on practice and health-related policies (Tyndall, 2008). Data integrety and subject protection are important issues in safeguarding study participants and IIT quality (Bhatt, 2011). Many international and national guidelines stipulate the need for a quality management system (QMS) (Houston et al., 2018). Serious incidents triggered the formation of these systems, e.g., experimental medicines in the United Kingdom in 2006 and in France in 2016 that had unexpected adverse effects for volunteers. It is widely argued that ethical review of medical research proposals is in itself insufficient to protect the rights and welfare of human subjects. The actual conduct of research requires supervision (Heath, 1979; Walsh et al., 2005; De Jong et al., 2013; Grit & Van Oijen, 2015).

Monitoring is essential to guarantee patient safety, data integrity and to detect serious problems, near incidents or weak spots – i.e. has informed consent really been realized, are data analyzed in time to check for unexpected trial results. Monitoring provides a consolidated source of information showcasing the progress of a clinical trial by collecting, distributing and analyzing information related to the objects of a trial, and the data gathered often generates (written) reports that contribute to transparency and accountability.

European Union (EU) guidelines require sponsors to monitor the conduct of clinical trials, so if a hospital sponsors a study, the hospital must monitor it (European Parliament and of the Council of the European Union, 2005). In recent years, regulations governing IITs have become increasingly complex, placing a greater burden on hospitals in terms of compliance, documentation, and training investigators (Glickman et al., 2009). In 2018, the Dutch Research Council (NWO) released a new code of conduct for research integrity, defining an organization's duty of care to provide a working environment that promotes good research practices. A severe incident, the 2008 Propatria study, caused the Dutch Health and Youth Care Inspectorate (IGJ) to focus on

IITs and raise awareness among the hospitals' Boards of Directors (BoDs) of their responsibilities as sponsors (Inspectie voor de Gezondheidszorg (IGJ) et al., 2009; Van Oijen et al., 2020).

According to the results of an investigation into the Propatria study, all hospitals must implement QMSs such as monitoring (IGJ et al., 2009). On-site monitoring is legally required in the Netherlands, but the second legislative evaluation of the Medical Research Involving Human Subjects Act (WMO) observed that this can be difficult to achieve. There are few practical guidelines or operational methods for quality management of IITs, and national or international supportive scientific evidence is scarce (De Jong et al., 2013). Researchers also find it difficult to find impartial monitors and meet the steep costs of monitoring (Stukart et al., 2012). These problems occur less often in commercial clinical trials, as funding from the pharmaceutical industry often enables extensive, structured quality management.

In clinical practice and in EU guidelines such as ICH E6 Good Clinical Practice[22], monitoring is seen as a standard for quality assurance of ongoing trials. However, to cope with the complexity and cost of organizing a QMS, some Dutch hospitals have implemented monitoring programs which more resemble the learning tradition of mentoring. Such mentoring programs are modeled on the practice of visitation established in the early 1990s to improve the quality and safety of patient care (Heaton, 2000). Mentoring programs introduced for medical students and doctors are regarded as key to successful and satisfying careers in medicine (Frei et al., 2010).

Our study aimed to investigate how hospitals in the Netherlands have developed and implement QMSs for IITs. We have chosen to make a theoretical distinction between two ideal-typical styles of quality assurance, which may be more or less intertwined in practice: (a) a professional perspective on quality improvement and/or assessments in hospitals with a focus on mentoring and peer review, and (b) a regulation perspective on clinical trials which need quality assurance systems like monitoring. Applying

[22] International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). (1996). ICH harmonized tripartite guideline. Guideline for good clinical practice: Consolidated guideline; E6(R1), 10 June.

this distinction enables us to interpret the approaches found in various hospitals. Mentoring and monitoring are not only theoretical terms, they also have legal significance as "monitoring" is the preferred system in the regulations. To make the distinction clear in this paper, we use italics to indicate the theoretical notions and refer to the legal notions in normal font. Note also that regulatory practices are now creating more room for alternatives to *monitoring* (Chilengi et al., 2010; Molloy & Henley, 2016).

The research questions we sought to answer were: How are *monitoring* and *mentoring* systems of investigator-initiated trials organized in Dutch hospitals, how do they function, and what are the consequences for learning processes and quality assurance of data management?

Theoretical framing of monitoring and mentoring

In the past decade, there has been renewed interest in the quality of IITs in hospitals. For our analysis, the term quality management includes aspects of overall hospital management that determine and implement the policy and quality objectives for IITs (adapted from Manghani, 2011). Two ways of organizing quality management are *monitoring* and *mentoring.* Our focus is on the work of monitors and mentors who:

- work at a hospital on the local or regional level;
- are responsible for control and/or support;
- and are required to periodically supervise researchers on-site (adapted from De Grauwe & Carron, 2007).

Both monitoring and mentoring are associated with ensuring compliance with local and international regulations and the policy statements of organizations designed to protect human subjects (Weijer et al., 1995; Korenman, 2006; Apau Bediako & Kaposy, 2020). However, there is little empirical evidence to determine which methods of trial monitoring are consistent with the ICH E6 guideline or how it applies in different clinical trial settings (Morrison et al., 2011). The past decade has seen a significant rise in the number and complexity of clinical trials worldwide and, with this increase, a shift to a more risk-adapted approach. The European Medicines Agency (2013) and the US

Food and Drug Administration (2013) have published papers on the merits of risk-based *monitoring* that permit a more targeted, flexible, and inexpensive approach (Molloy & Henley, 2016) that also leaves room for programs that resemble *mentoring*.

Monitoring

A clinical trial monitor checks whether adverse events are reported, and primary data are collected and recorded properly. Monitors meet periodically with the researchers to review their study records (Korenman, 2006). *Monitoring* is intended to educate research staff, provide quality assurance, and prevent research misconduct (McCusker et al., 2001).

According to Weijer et al. (1995), research *monitoring* includes four categories of activities: (1) continuous (annual) review, (2) monitoring the consent process, (3) monitoring adherence to protocol, and (4) monitoring data integrity (Lavery et al., 2004). Important aspects of *monitoring* are:

(1) it is part of management, not something added from outside;
(2) it is a continuous process, not a single operation;
(3) it has to do with collecting information to identify strengths and weaknesses and make proposals for action;
(4) it is result-oriented, thereby implying a clear, measurable definition of expected results;
(5) it results in an institutional action to solve problems and reach objectives (Richards, 1998; De Grauwe & Carron, 2007).

On-site *monitoring* may involve periodic site visits by a designated monitor, either internal or contracted (Molloy & Henley, 2016), who observes research procedures, reviews documentation, and in some cases interviews subjects and relevant research staff (Shetty et al., 2014; De Jong et al., 2013; Ochieng et al., 2013; Van Oijen et al., 2016, Apau Bediako & Kaposy, 2020). Each visit is followed by a report (Molloy & Henley, 2016).

The advent of risk-based *monitoring* in clinical studies has changed the traditional monitor's role significantly. Verifying source documents and transcriptions now consumes most of a monitor's time. The new role requires

analysis, data interpretation, and assessment skills; greater data-oriented communication capabilities; and the ability to learn and teach the basics of new technology to others (Cerullo et al., 2014).

A survey on knowledge and skill requirements for monitors suggested that general industry, ethics, and trial execution knowledge were critical for a monitor's work, followed by regulatory knowledge. The monitor needs to know basic GCP and trial protocol to ensure that the trial is adheres to the regulatory requirements. They also need to be familiar with the trial's Investigator's Brochure and the investigational product. These requirements are critical because they ensure that even in the absence of standard operating procedures (SOPs), a monitor can still perform well (Shah, 2012).

To sum up, *monitoring* is a continuous, result-oriented process, focused on compliance (consent procedures, adherence to protocol, data integrity) that leads to proposals for actions. In the process the knowledge of the monitor is essential (see Table 1).

Mentoring

The term mentor generally indicates a teacher, advisor, and role model (Jacobi, 1991; Kram, 1985; Nimmons et al., 2019). *Mentoring* involves a one-on-one, unidirectional relationship which pairs a novice (junior) with an experienced individual to receive guidance and support (Blackwell, 1989). Ideally, mentees and mentors engage as partners in reciprocal activities such as planning, acting, reflecting, questioning, and problem-solving (McGee, 2016). Pfund et al. (2016) emphasize that the research *mentoring* relationship occurs in a given social context which views both mentee and mentor as "learners":

(1) the mentee acquires research skills needed for scientific productivity and career-related knowledge;
(2) the mentor acquires a working knowledge of the mentee to nurture the academic and professional growth of the next generation effectively;
(3) both have the capacity to engage and find the "delicate balance between respect for tradition and openness to change" necessary to advance the field (Pfund et al., 2016).

Peer *mentoring* can be thought of as a response to traditional *mentoring*. It involves a two-way exchange between participants roughly equal in terms of age, experience, and/or position in their organization (Kram & Isabella, 1985; Angelique et al., 2002). While this mutuality limits career-enhancing functions in comparison to traditional *mentoring*, it significantly enhances psychosocial functions (Angelique et al., 2002).

Peer *mentoring* shows promise not only for the academic advancement of its participants, but also for fostering strong collegial and social relationships in the entire academic medicine community. However, it is important to consider its limitations. Participants of peer mentor groups may have less cumulative professional experience and thus a more limited advisory role than senior mentors (Bussey-Jones et al., 2006).

While the literature does report examples of peer *mentoring*, evaluations of the effectiveness of these groups are rare (Bussey-Jones et al., 2006). Implementing peer *mentoring* relationships should help increase the probability of junior faculty and clinicians becoming successful researchers. Johnson (2002) encouraged professional organizations to establish specific guidelines as a way of preparing mentors for their role and responsibilities. Moreover, *mentoring* needs structural and financial support (Johnson et al., 2010).

Baigent et al. (2008) and Chilengi et al. (2010) posit that any member of a clinical trial research team, such as nurses or data managers, can train as mentors and add this dimension to their roles. Mentor training can be organized in-house, at relatively less cost, as long as sufficiently experienced senior “monitors”/trainers are available.

To summarize, learning relationships are key in *mentoring*. The mentor helps researchers take charge of their own development and achieve results which they value (Connor & Pokora, 2012). In peer *mentoring* relationships, both the mentor and mentee learn (see Table 1).

Table 1 Contrasting monitor and mentor (adopted from Connor and Pokora 2012, p. 38)

Monitor (expert)	Mentor
Focus on compliance (Weijer et al., 1995; Korenman, 2006)	*Focus on feedback* (Rabatin et al., 2004)
Emphasis on knowledge	Emphasis on *mutual learning* process (Kram & Isabella, 1985; Angelique et al., 2002)
Expert insight is key	Helping skills are key
Puzzle-solver	Facilitator/enabler
Gathers/analyzes information	Enables information gathering
Facts and logic	Facts, logic, and feelings
Diagnoses the problem	Explores the problem
Objective definition of problem	Subjective definition of problem
Expert knowledge important	*Mentee* insight important

In this section, we presented the two approaches to quality assurance as ideal types, supposing that both can be combined in practice. In the following section we analyze if and how *mentoring* and *monitoring* are intertwined in *monitoring* practices for IITs.

Methods

Our previous research into public supervision of clinical trials in the Netherlands (Grit & Van Oijen, 2015; Van Oijen et al., 2020) alerted us to the incongruent development of *monitoring* practices for IITs, which if present, often do not function optimally. This prompted us to investigate the practice of *monitoring* and subsequently *mentoring*.

Research design

We used qualitative methods, supported by quantitative methods, to gain a better understanding of the perspectives of various stakeholders in IITs. First, we analyzed Dutch and international documents on quality management of clinical trials. We used this information to structure interviews (n = 26) and observations (n = 5) involving several actors: monitors and mentors, staff members, and the boards of multiple hospitals. The interviews focused on quality management of IITs (see topic lists in Appendix B).

The Netherlands has a three-tiered hospital system: general hospitals without training facilities, teaching hospitals, and university medical centers (UMCs). This study focused on UMCs (n = 8) and teaching hospitals (n = 26) because Dutch general hospitals rarely conduct IITs. UMCs, formed in the period 1983–2008 as mergers of university medical faculties and academic hospitals, receive special funding for research. The UMCs are members of the Netherlands Federation of University Medical Centers (NFU). Teaching hospitals have more recently started to participate in research projects but do not receive funding for this. They belong to the Association of Top Clinical Teaching Hospitals (STZ).

Our selection of hospitals for the interviews and observations was largely based on hospitals willing to participate. Because of the sensitive information discussed during *monitoring* visits, it was not always possible to obtain permission to conduct observations. It was often critical that staff members were willing to help us gain access, even for interviews.

In the period 2014–2018 we conducted interviews with a total of nine staff members (in one hospital two staff members), five members of BoDs, and one pair of monitors across 11 hospitals: four UMCs and seven teaching hospitals. We also conducted a series of interviews with supervisory bodies, namely the Central Committee on Research Involving Human Subjects (CCMO, n = 3, one employee twice) and the Inspectorate (IGJ, n = 5, one inspector three times). Interviews lasted 40–90 minutes and the processed data were shown to respondents for member check. In the Netherlands this kind of research requires no ethical approval.

After signing a privacy statement, we conducted five observations in one teaching hospital and two UMCs between 2014 and 2018. In one UMC, we observed three *monitoring* visits to low-risk studies performed by an external monitor: the initial visit, one interim visit, and the close-out visit. In one UMC, we closely observed a staff *mentoring* day during which five pairs of mentors monitored various studies (see topic list in Appendix B).

Our quantitative research consisted of an online survey that was sent to the BoD of each general or teaching hospital and the dean of each UMC in the Netherlands (n = 83). Some BoDs forwarded the questionnaire to a person responsible for quality management at the operational level.

In 2017 we emailed an invitation to participate in our study of quality management and quality assurance of IITs. The e-mail included a link to our online survey, explained the purpose of the study, and stated that anonymity of data was assured. A reminder was sent after a week. The questionnaire contained 36 multiple choice questions divided into five parts: [1] The respondent's situation (7 questions), [2] Numbers and finances (4 questions), [3] Quality assurance (11 questions), [4] *Monitoring* and auditing of IITs (12 questions), and [5] Finally (2 questions) (see Appendix B). The questionnaire was developed based on brainstorming sessions (n = 7) with the research team. The questionnaire was pilot tested by target participants (n = 2 including author WB) and adapted accordingly. In the questionnaire, we used the term *monitoring* because most hospitals used this term for their on-site quality management.

We compared our data with a survey conducted in the same target group in 2003. This survey focused on clinical trials of medicinal products and cooperation with the pharmaceutical industry. The respondents were UMCs (five out of eight; 60%) and teaching hospitals (24 out of 46; >50%) of which seven were STZ members (Van Oijen et al., 2007).

Data analysis

With permission, all interviews and observations (except for two of each) were recorded, transcribed, and coded. Qualitative analysis of the transcripts was performed independently by two investigators. We used Atlas.ti software version 8.0 (Atlas.ti Scientific Software Development Company, GmbH, Berlin, Germany) to analyze patterns in the data (see Table 2).

Coding (open, axial, and selective) was performed to examine the interrelationship of three main categories: a consideration of context, such as an UMC or teaching hospital setting; intervening conditions, i.e., the backgrounds of monitors, their goals, and methods utilized; and the effects

of these factors. We aimed to explore the differing purposes and designs of quality management of IITs, the role of monitors' and mentors' knowledge and experience, and the social relationships between stakeholders.

Table 2 Themes and their related codes

Themes	Codes
Interviews staff members	
Background staff members	-
Reasons to set up and implement a quality management system for research	Inspection visits, guidelines (sub)sector associations, assurance of data validity, mergers
Design of quality management system (and monitoring/mentoring)	Decision-making by BoD on advice of staff members
Roles, responsibilities, and escalation procedure between BoD and staff members	Defined or under development
Risk classification by guidelines (sub)sectors or MREC	Consequences for monitoring/mentoring clarified or under development
Qualifications of monitor vs. mentor	Expert (pharmaceutical industry experiences) vs. colleague (peers)
Training/knowledge exchange of monitors/mentors	By experts and peers, tailor-made, scientific meeting
Link with MREC for an overview of approved studies	Yes/no
Procedures for monitoring/mentoring	Frequency, different approach depending on risk classification, SOPs, formats, and templates or under development
Searching for pragmatic solutions	Starting from scratch, efficient organization mentoring visits (e.g., planning peer-to-peer visits or planning a few different visits each year)
Dealing with the gray zone	Translate regulation into research practice
Offering a data- and/or study-management system	Developed or under development
Providing support in mentoring system	Matching researchers, facilitating start and debriefing of a meeting, supporting decision-making, preparing or reviewing the report
Relationship management	Actively manage its relationships with the BoD, researchers, colleague staff members of other hospitals via (sub)sector associations
Key success factors	Support of the BoD, resources from the hospital, knowing your researchers, providing support to researchers (being in contact, answering questions), qualified monitors/mentors

Table 2 Continued - Themes and their related codes -

Themes	Codes
Monitoring vs. mentoring (observations/interviews)	
Guides the process of the meeting	Self-supporting vs. support from staff member
Clarifies goals of meeting	Self-supporting vs. support from staff member
Provides information and resources (SOPs, templates)	Self-supporting vs. support from staff member
Provides feedback	Open, directly, constructive, detailed, positive, critical
Support for their tasks as monitor/mentor	Self-supporting vs. support from staff member
Backbone	Knowing the essence of doing research by heart or using a checklist
Creating/facilitating a learning environment	For knowledge transfer (one-way) vs. mutual learning (two-way)
Factors that affect dialogue/collaboration/ interaction	Listening actively to each other, open-minded towards (new) ideas, asking clarifying and in-depth questions, power vs. equity, providing tips, explaining important concepts
Focus/relationship	Following regulation and problem-solving vs. a two-way flow of assistance and support
Reporting	Self-supporting vs. support from the staff member

These preliminary themes were compared and then revised through an iterative discussion process as we conducted further analysis. The research team discussed the data and incorporated feedback into final reports. Sampling was concurrent with data collection and analysis and proceeded until no further unique themes emerged from successive interviews (saturation). We became particularly interested in comparing and contrasting participants' experiences with *monitoring* and *mentoring*. The research design has thus sampled *mentoring* and *monitoring* practices from several different hospitals.

Results

In the Netherlands, as sponsors of an IIT, hospital BoDs are responsible for ensuring that robust QMSs are put in place. In practice, the methods used differ per hospital. It is important to clarify that in practice most hospitals use the term "*monitoring*" for their on-site quality management. However, after analyzing our results, we posit that some of their approaches can be more clearly defined as *mentoring.* We will use this term when we observe this.

After close examination of the results, three overarching themes were found: (a) organizing a QMS for IITs, (b) similarities and differences in the processes of *monitoring* and *mentoring*, and (c) creating a learning environment.

Organizing a quality management system for IITs

A QMS for IITs includes various components, such as training in GCP, developing guidelines and SOPs, and auditing or *monitoring*. This paragraph focuses on triggers to start designing and implementing QMSs and the BoD's role in this, especially concerning *monitoring*.

Triggers to start designing and implementing QMSs for IITs

All interviewed hospital members indicated that inspection visits and the Propatria incident were triggers to start designing and implementing their QMSs. The Propatria trial, a probiotic study of acute pancreatitis, was an IIT conducted in 15 hospitals, led by one UMC as sponsor. In the probiotic group 24 patients died from their disease, compared to nine patients in the placebo group. The subsequent investigation conducted by IGJ and CCMO, among others, highlighted several serious shortcomings in the design and execution of the research protocol, the information on side effects provided to the patients, and the reporting of serious adverse events (IGJ et al., 2009; Zaat & Leeuw, 2009). The Propatria report also revealed that the hospitals' BoDs failed to meet their responsibilities as sponsors according to the WMO. The safety of human subjects had been inadequately secured because several actors had not ensured that clear and efficient procedures were in place (IGJ et al., 2009).

As a result, the Netherlands Federation of University Medical Centers (NFU) released a new version of the document "Quality assurance for people-related research 2.0", aiming to harmonize standards of quality assurance based on the recommendations of the Propatria report. It stated that risk-based *monitoring* is an essential tool for quality assurance in human research and a responsibility of the BoD (Nederlandse Federatie van Universitair Medische Centra (NFU), 2012). All interviewed hospitals chose to take this risk-based quality assurance approach.

However, UMC staff members state that it is not easy to harmonize the NFU guideline. UMCs all have their own ways of implementing it:

> "We do have discussions with other monitors in the NFU, we want to share, but in the meantime we haven't shared anything yet [. . .]; everyone does it for themselves." (staff member, UMC I, 2017)

Sharing experiences is common in teaching hospitals because increasingly they wish to portray themselves as research actors, which used to be a privilege of UMCs. In 2014–2016, two teaching hospitals underwent an inspection visit focused on IITs. These hospitals shared their experiences with others in the association of non-university teaching hospitals, the STZ. One of their critical findings was the absence of an adequate *monitoring* system. This created a sense of urgency among teaching hospitals and prompted the STZ to undertake further supportive actions. In recent years, the STZ's work has focused on examining best practice among members to create SOPs, which hospitals can use to supplement their quality assurance manuals. In 2016, the STZ, which is responsible for admission and reaccreditation criteria for teaching hospitals, launched a new stipulation: the hospital needs to have a functioning *monitoring* system for any research subject to the WMO.

In sum, the Propatria incident and the inspection visits prompted change in hospitals. As a result, BoDs became more aware of their roles and responsibilities concerning QMSs for IITs. Moreover, sharing knowledge and the support of their (sub)sector associations were critical for enacting it.

The BoD's role in organizing a QMS for IITs

The 2003 survey, conducted three years after the WMO was introduced, showed that BoDs had only modest designs for the execution of their formal roles and responsibilities. UMCs, teaching hospitals and STZ members outlined a clearer picture of the nature and extent of clinical drug trials performed in their hospital than other non-STZ teaching hospitals. Only UMCs could provide financial insights. BoDs were advised not to limit their role to a "paper exercise". A clear interpretation of their role was desirable, as well as the necessary practical and support facilities to monitor progress (Van Oijen et al., 2007).

In 2017, four out of eight UMCs and 18 out of 26 teaching hospitals began the second online questionnaire, which three UMCs and 16 teaching hospitals nearly completed. This survey showed that all responding UMCs and teaching hospitals provide financial support for their own IITs. Most can provide information about the number of IITs performed annually, have policies for clinical trials, and have the support of a science bureau or advisory committee for the coordination and/or implementation of quality assurance.

In general, nearly 25% (n = 4) of BoDs never receive a report on quality assurance of IITs, almost 25% (n = 4) receive one a year, nearly 50% (n = 8) receive 2–10 reports each year, and only 5% (n = 1) receive 10–20 reports each year. Of the BoDs 80% (n = 21) spend 1 hour or less per week on quality assurance of IITs, almost 15% (n = 3) 1–2 hours per week, and only 5% (n = 1) 2–4 hours per week. More than 60% (n = 13) of the BoDs rate themselves as having sufficient knowledge and skills but almost 40% (n = 8) rate themselves as neither sufficient nor insufficient.

Other results of the online survey show that all UMCs and 70% of the teaching hospitals perform *monitoring* activities based on legal standards, sector and (inter)national guidelines such as the ICH GCP, and hospital-based guidelines. All UMCs and 60% of the teaching hospitals use risk-rating for IITs. In all UMCs, *monitoring* is performed by professionals with sufficient expertise in conducting research and in teaching hospitals by professionals as well as data managers or research nurses. UMCs mostly have 5–10 monitors (n = 2; >60%) or 10–20 monitors (n = 1, >30%), and teaching hospitals fewer than 5 (n = 12, >70%) or 5–10 (n = 4; almost 25%). All UMCs support their monitors with training and evaluation. Teaching hospitals give support by training in 70% (n = 12) of cases and by evaluation in 40% (n = 7). Only one UMC (>30%) and three teaching hospitals (almost 20%) collaborate with one or more hospitals in the field of *monitoring* of IITs.

The practice of two systems of quality management: Monitoring *and* mentoring

In practice, all hospitals search for pragmatic solutions to organizing their QMSs for IITs, depending on the frequency of research, history of their hospital, their experiences with clinical trials, and available resources. Most

UMCs, which often conduct government-funded research, have *monitoring* systems in place. Our research shows only one of three UMCs starting to build a *mentoring* system in 2017. Most teaching hospitals, with no additional funding from the government, have chosen to implement a *mentoring* system. Discussing the outcome of an inspection visit, a BoD member of a teaching hospital explains:

> "The most important issue was actually improving patient data monitoring during a trial. Look, we don't get direct government funding [like the UMCs], so we started with pragmatic solutions, like in monitoring, the researcher from one study verifies another study and vice versa." (interview BoD member, teaching hospital VI, 2018)

We found several ways of financing the *monitoring* or *mentoring* system. In two UMCs, *monitoring* is performed by full-time monitors in a staff department. In one of these UMCs, the BoD bears the cost of the monitors, while in the other UMC various departments share the cost. In all other cases, where *mentoring* is done by a peer (e.g., a researcher, research nurse, or data manager), financial affairs are arranged through closed stock exchanges in departments; each department must deliver a peer.
There were three strikingly different BoD roles in supporting quality assurance. First, in the UMC whose BoD funds permanent monitors, this "huge" support gave staff the chance to design the system from scratch and implement it properly.

> "If things aren't going well and what you say is valuable, you need the right people [BoD's] behind you. Because otherwise you can yell whatever you want, but if nobody does something with it, it's pointless." (staff member, UMC III, 2016; monitoring system)

Second, in another UMC, a new BoD decided to launch a *mentoring* pool. All medical departments are responsible for ensuring the participation of mentors in this *mentoring* program. If a department does not deliver a mentor for the pool, the staff member responsible for organizing *mentoring* must request the BoD to contact the chair of this department. The staff member uses the authority of BoD to enforce change.

> "In the beginning I thought, what an exaggerated hassle, [. . .] but I found out that they don't listen if it's just me." (staff member, UMC I, 2017; recently started a mentoring system)

Third, in cases of minimal contact and support from the BoD, a QMS cannot flourish. Staff can use documents prepared for IGJ visitations to inform the BoD about the current state of affairs.

> "I don't often have one-on-one conversations with the BoD. For the past two years the BoD has just been busy with the merger. [. . .] Providing data for the Inspectorate, that just opens doors [. . .]. When I had to send the documents to the Inspectorate, I made a nice email for the BoD: this was my approach, these are the shortcomings. Now they are well-informed, if the Inspectorate decides to visit us." (staff member, teaching hospital III, 2016; orienting towards a mentoring system)

This staff member recently received an external two-year grant to start *mentoring*. The hospital will appoint a staff member to coordinate *mentoring* for four hours a week, train mentors, and offer on-the-job training. As a result, the staff member strengthened their own position and brought *mentoring* to the attention of the BoD.

Overall, these findings show that the BoD is crucial in terms of financial and decision-making support. The choice of a QMS and its design is often based on the advice of staff members. Moreover, when problems arise, staff members do not have the overriding authority and are dependent on the organization, the BoD, to create opportunities that enable them to work on quality assurance. In practice, the responsibility of implementing a *monitoring* or *mentoring* system is delegated to staff departments as they are in charge of quality control, improvement, and assurance of IITs.

Similarities and differences in monitoring and mentoring processes

To categorize the practices of on-site QMSs, we looked at the designated monitor or mentor and the focus of their approach.

Most of the eight hospitals involved have an approach dominated by either *monitoring* or *mentoring*. Specifically, one UMC and three teaching hospitals work with a *mentoring* system, one UMC with a *monitoring* system, and one UMC with mixed methods. One teaching hospital that has been working with a *monitoring* system is reconsidering. Another teaching hospital, yet to develop a QMS, is leaning toward *mentoring* (see Table 3 for a summary of key elements of each hospital. For a more detailed description, see Table 3 in Appendix B).

In general, both *monitoring* and *mentoring* approaches focus on the researcher's knowledge, skills, and behavior with respect to responsible conduct of research. In practice, we found similarities and differences in these processes. On-site visits for both *monitoring* and *mentoring* include face-to-face meetings with a researcher. One important difference is the frequency of meetings. In a *mentoring* approach, a peer visits each research study at least once and in some cases a staff member does the follow-up. In a *monitoring* approach, there are several meetings: the initial visit, a *monitoring* visit and a close-out visit. The way these visits are conducted depends on the risk involved and the study design e.g., when the first human subjects are expected to be enrolled.

Another similarity deals with what respondents call the gray zone. All interviewed staff members trained as monitors stated that GCP-qualified researchers need practical help to translate legal requirements to their own research practice. The work of both monitors and mentors is focused on the interpretation of rules, and this has far-reaching implications for practice.

> "We're working in that gray zone all day. How much do we need to do to comply with the rules, and how do we keep things workable? [. . .] We know some things are sometimes not entirely up to the code, because you know the researcher does not have the resources or time to do that. Sometimes it's tough and because of that there is no complete risk coverage. [. . .] You have to take that for granted." (staff member, UMC III, 2016; monitoring system)

Table 3 Characteristics of hospitals, a summary of key elements

	UMC I [2017]	UMC II [2016]	UMC III [2016]	Teaching hospital I [2015–2016]	Teaching hospital II [2018]	Teaching hospital III [2016]	Teaching hospital IV [2018]	Teaching hospital V [2018]
Chosen system	Mentoring, recently started	Monitoring and mentoring	Monitoring	Mentoring, recently started	Monitoring; (re)thinking/ (re) considering the system	Orienting toward a mentoring system	Mentoring	Mentoring
Detailed description	Two mentors work together to mentor one research study during a central organized mentoring day (peers)	Nine divisions have provided money for central monitoring with which two centrally appointed external monitors are temporarily appointed and paid. In the other three divisions, monitoring is done by self-trained personnel. Research with minimal risk is monitored by a research nurse or BROK*-qualified researcher (mentoring)	Monitors, most with a pharmaceutical background, are a part of a staff department	Peer-to-peer mentoring with two researchers assessing each other's study	Monitoring; (re)thinking/ (re) considering the system	Mentoring (planned). At this moment, no policy, programs, or structures available; building on the experiences of teaching hospital I	Mentoring is done by a research nurse	Mentoring, building on the experiences of teaching hospital I
Recruitment, managing, and support of monitors/ mentors	Staff department; recruitment by department (obligatory)	Staff department; recruitment by department (obligatory)	Staff department; working with internal monitors	Staff department; recruitment by department (obligatory)	Staff department	Staff department	Staff department	Staff department

*BROK: Basic course in regulation and organization for clinical researcher

To act in this gray zone, a staff member of teaching hospital IV explains that "you need to be tolerant" and "it's a process of give and take" to steer researchers in the right direction. "The reality is that patient care always comes first. It's the primary task of medical specialists." However, this staff member shared her realization, while observing an Inspectorate visit, that even if you inform all the parties concerned, you cannot take for granted that they will adhere to agreements: researchers sometimes work outside the zone of what is acceptable:

> "Then I learned that documents could simply end up archived at another participating hospital. Whereas we all know [. . .] the material must actually stay in the hospital [...] and can't be archived outside the hospital for 15 years without our BoD knowing about it. If you discuss it and record it, that's something else [. . .]. They didn't take those steps." (staff member, teaching hospital IV, 2018; mentoring system)

Monitoring processes

In a *monitoring* system, the monitor belongs to a separate staff department, and being a monitor is their profession. With a workload of 60–80 studies, the independent monitor arranges appointments with researchers, answers their questions, prepares the reports, and has periodic consultations with their colleagues and supervisor. The selection and matching of research studies to a monitor depends on which department is paying or on the monitor's interest or field of expertise.

During our observations we found that monitors are result-oriented, meaning that they thought that a study should be conducted in accordance with protocol and regulation. Monitors are also need-driven, meaning that monitors put the needs of the researcher first and give the researcher the feeling that they have all the time in the world. Our observations of a *monitoring* visit and close-out visit reveal that the monitor encourages an atmosphere open to learning. The willingness of the researcher and the reciprocal trust between the two are important. There is a clear division of roles and this colors the learning process and what is discussed on each visit (see Creating a learning environment).

> The monitor regularly advises the researchers on how to deal with guidelines, legislation, or the Medical Research Ethics Committee (MREC). And each time, the acquisition of knowledge and skills is paramount. Given this advice, the researcher responds immediately e.g., by revising the title of a document, printing it out and putting the hard copy in the Trial Master File, or updating a randomization list. Clearly and comprehensively, the monitor gives pointers on how to improve the study documentation, such as where to find supporting material on the hospital's intranet. It was noticeable that the doctoral researchers found this tailor-made advice very welcome. (Observations during several *monitoring* visits UMC II, 2016)

Table 4 summarizes the characteristics of *monitoring*.

Mentoring processes

The findings regarding *mentoring* contrast with *monitoring*. The mentor is task-oriented, goal-driven, and concentrates on the filling out a reference list based on ICH GCP. Backed by this checklist, the mentor focuses on asking questions to clarify how a situation has arisen and to analyze critical moments in a study.

Next we show a case of peer-to-peer mentoring, with two researchers assessing each other's studies. This meeting was one of the first arranged by the staff member of teaching hospital I. Other hospitals adopted this process (see Table 3) which turned out to become a best practice.

> The introductions are spontaneous, led by the staff member, as the researchers arrive in turn. We can't shake hands because the one is loaded down by six folders of study-related material, while the other is carrying two folders and, it turns out later, a USB stick. [. . .] The staff member explains the purpose of the meeting, hands out the reference list (see Appendix B) and answers questions about the *mentoring* process. The researchers jokingly promise to write neatly so that the

> staff member can draw up reports based on their data. After the researchers agree to call the staff member when they have finished *mentoring*, she leaves the room.
>
> The reference list topics direct the conversation. The peers discuss both studies for each topic on this list, so they continually switch in their roles of mentor and researcher. Sometimes an item on the list leads to a fuller discussion which often helps to create better understanding. Afterwards, the peers submit their notes of matters that remain unclear to the staff member.
> Both consult their folders intensively. This is difficult because the layout is not uniform. When the mentor cannot find the MREC approval for a protocol, the researcher looks for it himself; he cannot find it either. In the first instance, the mentor marks this topic "no". The researcher then checks whether he has saved the approval on his USB. As soon as he finds it, he sighs in relief. He prints the document and adds it to the folder and the mentor corrects his finding to "yes". After two hours, they have completed the reference lists and call in the staff member. (observation notes, peer-to-peer *mentoring* session, teaching hospital I, 2015)

In general, on a peer-to-peer *mentoring* visit, the focus is on training, supporting, problem-solving, and encouragement (Edwards et al. 2014). Learning is a two-way process. The mentor has more experience in a specific field or research practice, which can be accessed when needed.

> In a peer-to-peer *mentoring* session between two researchers, a physician and a trainee pharmacist, the latter shares his experience. He says that the pharmacist's curriculum vitae should be included [in the report]. A pharmacist usually provides several signed and dated CVs because they are often requested. (observation notes, peer-to-peer *mentoring* session, teaching hospital I, 2015)

Since the *mentoring* system is managed professionally by a staff member to avoid bureaucratic obstacles, a *mentoring* visit is well-organized and can be held in a limited time period. First, the most important criteria for matching

mentors with researchers is that they should not have worked together often. Second, the staff member facilitates the start and debriefing of the session and gives support at the end. Third, the staff member is responsible for preparing or reviewing the report, and sometimes verifying the implementation of its recommendations.

> During the debriefing at the end of the *mentoring* session the staff member checks if the forms have been filled in completely and the handwritten notes are legible and promises to write up the report quickly and submit it to the mentor for approval. (observation notes, peer-to-peer *mentoring* session, teaching hospital I, 2015)

Table 4 summarizes the characteristics of *mentoring*.

Table 4 Characteristics of mentoring and monitoring in practice

	Monitoring	Mentoring
Profession	Being a monitor is their profession; a monitor works on 60–80 studies on average at a time.	Being a mentor is a side activity for members of a research team; a mentor periodically takes on one study.
Hierarchy	A monitor is an expert, often with experience in the pharmaceutical industry, who has a professional understanding of regulations.	A mentor is a colleague, who has experience with and knowledge of daily research practices.
Structure	Each research study is visited several times: initiation, monitoring, and close-out visit. Result-oriented.	Each research study is visited at least once by a peer and in some cases a staff member does the follow-up. Research-process oriented.
Focus	Explication, compliance with (inter)national standards, and immediate correction. Focus on procedural information, the practical application of knowledge, and the policy principles of the organization.	Training, problem-solving, support, and encouragement to comply with (inter)national standards. The focus is on the practical implications of doing research and increasing work-related fulfillment.
Support	Monitor is self-supporting. Support from colleagues (monitors) and/or staff members upon request.	Support from staff members during (peer) *mentoring* is crucial to decision-making, reflection, and reporting.

Creating a learning environment

Creating a learning situation is fundamental to both *monitoring* and *mentoring* approaches. However, the way it is created differs.

Monitoring in practice

In a *monitoring* approach, the monitor tries to create an environment in which fosters knowledge transfer (UMC II, 2016); see Box 1.

Box 1. How the monitor fosters knowledge transfer during an initiation visit in UMC II (2016)

- uses a PowerPoint presentation to give "this meeting some structure and to make sure everything is discussed."
- takes time to introduce herself and show her expertise as a monitor: "I work with a colleague and we both monitor about 80–85 low-risk studies."
- explains the purpose of monitoring.
- uses humor to create a relaxed atmosphere: "So if you call me and I don't recognize you, it's because I hear a lot of names [laughing], it has nothing to do with you."
- provides room for the researcher to participate: "Here is a slide for you, if you want to say something about it [study design, in/exclusion criteria, end points, number of human subjects, recruitment], not as a test, but to hear you say it in your own words. If you don't know things you can leave them out."
- gives examples to explain important concepts: "There are times when you might deviate from the protocol. One is a protocol violation, which has a major effect on your data or your human subject. For example, you could [accidentally] include an underage person. Suppose you didn't know that this person was not 18 yet, only 17, but still included. This would be a violation that you'd describe on a violation form. These forms always go to the MREC."
- presents substantiated tips that show her understanding of the essence of doing research and the importance of 'following the rules': "If you work with student assistants, they should know the protocol. As a researcher you should train them to understand this protocol. You can also register the training register to show they were there, signed the list, and they have heard it. Then you can always refer to it, if things are going on: you were at that training session. I explained it there. So, you always know what someone should know."
- promotes standard procedures: "We monitors have been successful in getting researchers to work with standard content in a Trial Master File, using differently colored tabs."
- checks how the study will be conducted in practice, which produces information on the research program which is not immediately apparent from the protocol.

Finally, the monitor provides lots of room for the researcher to ask questions, such as "Should we save [in digital form] draft versions of approved documents of the Patient Information Form?" (researcher at the initiation visit, UMC II, 2016; monitoring system)

During the visits, the monitor focuses on explication, compliance to (inter)national standards, and immediate correction. To do so, the monitor scrutinizes the trial master and study files in proximity to the researcher. Sometimes the monitor and researcher work shoulder-to-shoulder in the same room and sometimes the monitor works in a separate room close to the researcher. The proximity of the monitor creates a certain interaction. When an issue arises, the monitor tries to unravel it by checking the protocol or SOPs. If the issue remains unresolved, the monitor discusses it with the researcher as soon as possible. As a result, these matters are not mentioned as action points in the report. Each finding is used to build a learning setting in which the expert knowledge of the monitor is key (observations of various *monitoring* visits UMC II, 2016).

Per hospital, the BoD budget pays for the support and training of researchers. Especially in UMCs with a *monitoring* system, staff departments provide additional opportunities. A staff member of a UMC explains:

> "We can give a tailor-made training, and every month we organize info lunches for a group of some 20 researchers and talk informally about informed consent, for example. So, for us, [we are] a bit of a [conduit] mouthpiece to the researchers, maintaining relations and increasing their knowledge. [The researchers are very enthusiastic (about the training)]." (staff member UMC III, 2016; monitoring system)

In sum, the monitor creates an environment which facilitates knowledge transfer. It involves encouraging a deeper processing of the essentials of "doing research" by questioning how knowledge can translate into action (following regulations) and identifying gaps that need to be closed (problem-solving). Table 5 summarizes the learning perspectives of *monitoring*.

Mentoring in practice

Most teaching hospitals have chosen to develop a *mentoring* system, which emphasizes learning and improvement. At least one visit is conducted in most *mentoring* systems, but learning remains a priority, as a UMC staff member who recently implemented a *mentoring* system explains:

> "It sounds exaggerated, but in the beginning we certainly want to monitor everything, to get to know the departments [and] it sounds a bit rude, but we also have to train. Researchers need to become aware that [it] is not only about the approval of MRECs. There's more to it, you have to be educated, [. . .] you know, your data has to be well-organized." (staff member UMC I, 2017; mentoring system)

Since 2016, UMC I organizes periodical *mentoring* days. The mentors are allocated proportionately by each department and paired mentors (peers) work together to mentor a researcher's study. The staff member allocates time for the mentors to swap knowledge and experiences at the start and during the lunchtime meeting. This staff member emphasizes the two-way learning in *mentoring*:

> "Learning is important, because what monitors see, they take to their own workplace." (staff member UMC I, 2017; mentoring system)

During our observation of a peer-to-peer *mentoring* session between individuals on the same level of research experience, we noticed that a reciprocal flow of assistance and support (Keyser et al. 2008). In this two-way relationship, learning from and with each other is a crucial point.

> The *mentoring* visit starts with an introduction to the studies and both researchers fill in their study data on the list. Filling in the reference list creates equal standing, because both researchers do so in their role of mentor. The roles change frequently as both researcher and mentor often "sit in each other's seats" to help and learn from each other and ensure that the list for their IIT is filled out as well as possible. In their role as mentor, they both ask interested, in-depth questions, aimed at really wanting to understand how the study works and what exactly has happened so far. For example: have they tabled any amendments, and if so, why? How did the one-year follow-up go? Are all the human subjects still alive? One researcher shows some uncertainty while filling in the list. In the role

> of mentor, the other researcher takes the lead and helps him in a collegial manner. No role confusion was noted. (observation notes, peer-to-peer *mentoring* session, teaching hospital I, 2015)

The staff member facilitates the start of a *mentoring* meeting and the debriefing at the end of the *mentoring*. The staff member has a crucial role in resolving issues, giving advice to support decision-making, and helping the researchers reflect.

> During the debriefing of a peer-to-peer *mentoring* meeting, the mentors discuss any remaining questions with the staff member, e.g., what does 'trial agreement' mean? The staff member explains that a trial agreement is required for a multicenter or industry-funded trial, so [in their case] the mentors should put "not applicable". (observation notes, peer-to-peer *mentoring* session, teaching hospital I, 2015)

In most teaching hospitals, the staff member already provides or is developing training facilities for mentors. At least once a year, teaching hospitals need to organize a scientific meeting and/or innovation symposium, due to STZ admission and reaccreditation criteria.

In sum, *mentoring* is focused on two-way (mutual) learning by mentor and mentee. By offering constructive feedback the staff member ensures that the research follows the standards (reference list) and creates a learning environment by encouraging reflection on practice, performance, and experience. Moreover, the staff member facilitates a collective learning environment via scientific meetings and symposia. Table 5 summarizes learning perspectives of *mentoring*.

Table 5 Learning perspective in monitoring and mentoring

Monitoring	Mentoring
One-way learning: from monitor to researcher	Two-way learning: mentor and researcher both learn (Merrick 2005)
'Supervision' perspective	Collaboration perspective
Hierarchical relationship. Apply "master-pupil" model as a powerful teaching method to transfer knowledge	Non-hierarchical relationship (Morton-Cooper and Palmer 2000). Focus on equality can be a simple and effective to enhance learning efficiency

Discussion

In the Netherlands, due to adverse incidents, the critical findings of Inspectorate visits and stricter regulations, BoDs are taking up their responsibility to provide an adequate QMS for IITs, as well as policies to meet (inter)national ethical and legal standards. Hospitals are challenged to develop innovative models to advance the quality of data of IITs given constrained resources.

In theory, we can classify the different approaches in developing QMSs for IITs in two ideal types of *monitoring* and *mentoring*. Both monitoring and *mentoring* are associated with ensuring compliance with local and international regulations, but according to the literature, they are different pathways to reaching that goal. In *monitoring* the monitor's knowledge is essential, leading to result-oriented proposals for actions, whereas mutual learning processes to solve problems are imperative in *mentoring*.

According to the theory, both systems require a certain degree of supervision to ensure compliance with regulations, laws, and hospital policies. However, contrary to the theory, both systems create a culture focused on awareness and learning; two vital aspects of quality assurance, as is known from research into safeguarding the quality of care (Alingh et al., 2015). The ways in which learning is accomplished, however, differ between the two models.

In a *monitoring* setting, learning is mostly one-way, from monitor to researcher. Due to their knowledge and expertise, monitors have a substantial ability to create a meaningful research environment. They establish this step-by-step, using several ways to create an atmosphere in

which learning can take place, with learning focused on “how to behave”, because the one who is monitored must learn how to follow “the rules”. In other words, on the various visits, especially the initiation, monitors facilitate knowledge transfer by developing a relaxed atmosphere, explaining important concepts, giving substantiated tips, and explaining how to find supporting materials. Adding to Connor and Pokora (2012), the emphasis of *monitoring* is on knowledge transfer (see Table 1).

In a *mentoring* setting, the learning culture is horizontal. The equal relationship between a peer mentor and researcher can simply and effectively enhance mutual (two-way) support and learning. To ensure that learning experiences are retained in this kind of temporary, task-oriented relationship, it is important that peers express what they have learned and what they will bring to a new *mentoring* setting. Otherwise, the experiential expertise of a mentor remains unused and the organization cannot learn from it either. Moreover, staff members trained as monitors play an important role as advisors. They are responsible for the organization and time management of quality assurance activities and fulfill all kinds of duties.

Although hospitals have traditionally invested in the quality assurance of healthcare, which includes both *monitoring* and *mentoring* practices, quality management of IITs seems to be less embedded due to limited resources and attention. The resources and support of a hospital’s BoD is an influential factor in the choice between taking a *monitoring* or *mentoring* approach. Funded by the government, most UMCs have a *monitoring* system in place. Most teaching hospitals, with no additional funding from the government, have chosen a *mentoring* system. The costs of *monitoring* and *mentoring* IITs are likely to be borne by the organization: centrally (BoD) or locally (clinical research departments). Not always financial, costs may also include the working hours a department must make available. *Mentoring* always requires local contribution or can be settled on mutual terms, whereas this is not always the case for (central) *monitoring*.

Our study reveals the critical impetus of the relationship between the BoD and staff members. Staff can play a decisive role at moments of uncertainty about quality management by advising on and constructing an appropriate path of development. Moreover, the power and authority of the BoD is needed for full efficacy in tackling such problems as mentor recruitment.

We noticed that both BoD as sponsors of IITs and staff struggle with the same problems in both systems because on-site *monitoring* or *mentoring* alone can never guarantee high quality of IITs (Brosteanu et al., 2009). Our analysis shows that in practice, even when hospitals choose for either of both systems, a combination is used. To strengthen the QMS of IITs and provide a working environment that promotes good research practices (research integrity), this means finding a balance between; forms of quality assurance and limited resources, organizing "another set of eyes" and addressing researchers' own responsibility and expertise, and checking compliance and creating an open culture of learning. Such balancing entails designing a QMS that sues the strengths of both monitoring and mentoring. The challenge then is to maintain an integrated view ensuring sufficient coherence between the components of a QMS; that is, finding a balance between accountability and learning (De Grauwe & Carron, 2007).

As this requires sponsors to take a risk-based approach, the BoD needs to cope with this challenge (EMA, 2013). Although all *mentoring* practices are based on the NFU risk classification, it remains unclear whether *mentoring* is a more flexible and less costly approach (Chilengi et al., 2010; Molloy & Henley 2016). Also unclear is if mentoring complies more or less with regulation than monitoring. In our view, it takes creating robust systems, spreading best practices on quality management strategies among hospitals, and sharing experiences through cooperation and partnerships. For both UMCs and teaching hospitals, their (sub)sector associations can play an important role.

Limitations

Our study has several limitations. Although we used a mixed dataset derived from interviewing stakeholders, observing *monitoring* and *mentoring* activities, and an online survey of BoDs, the validity of our conclusion might

still rest on a relatively small focus on the Netherlands. However, we believe that our findings may be relevant for organizations in other countries facing the same challenges concerning the *monitoring* of IITs, because lessons can be learned from analyzing different practices and exchanging experiences. Another limitation is that we have no systematic data to determine in detail the effectiveness or efficiency of various approaches. More research is needed to assess the potential impact of the variations in the *monitoring* practices observed (Morrison et al., 2011).

In conclusion, conducting clinical trials in resource-limited settings can be challenging given the regulation requirements for ongoing IITs. Moreover, uncertainty about what is necessary to comply with regulation further complicates the development of an accurate QMS. Our data show that *mentoring* can be especially beneficial in resource-limited settings, such as teaching hospitals, as a pragmatic, vital first step in quality management to ensure reliable and accurate scientific results. Hospitals are balancing between *mentoring* and *monitoring* as they attempt to seek a trade-off between concentrating expertise within a small staff department and developing a hospital-wide culture of learning and support (Brosteanu et al., 2009), which fits their traditions and resources.

Chapter 5

Boundary work to improve productive research collaboration and to achieve research impact

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Abstract

Background

In the Netherlands, university medical centers (UMCs) bear primary responsibility for conducting medical research and delivering highly specialized care. The TopCare program was a policy experiment lasting four years in which three non-academic hospitals received funding from the Dutch Ministry of Health to also conduct medical research and deliver highly specialized care in specific domains. This study investigates research collaboration outcomes for all Dutch UMCs and non-academic hospitals in general and, more specifically, for the domains in the non-academic hospitals participating in the TopCare program. Additionally, it explores the organizational boundary work employed by these hospitals to foster productive research collaborations.

Methods

A mixed method research design was employed combining quantitative bibliometric analysis of publications and citations across all Dutch UMCs and non-academic hospitals and the TopCare domains with geographical distances, document analysis, and ethnographic interviews with actors in the TopCare program.

Results

Quantitative analysis shows that, over the period of study, international collaboration increased among all hospitals while national collaboration and single institution research declined slightly. Collaborative efforts correlated with higher impact scores, and international collaboration scored higher than national collaboration. Sixty percent of all non-academic hospitals' publications were produced in collaboration with UMCs, whereas almost 30% of the UMCs' publications were the result of such collaboration.

Non-academic hospitals showed a higher rate of collaboration with the UMC that was nearest geographically, whereas TopCare hospitals prioritized expertise over geographical proximity within their specialized domains.
Boundary work mechanisms adopted by TopCare hospitals included aligning research activities with organizational mindset (identity), bolstering research

infrastructure (competence), and finding and mobilizing strategic partnerships with academic partners (power). These efforts aimed to establish credibility and attractiveness as collaboration partners.

Conclusions

Research collaboration between non-academic hospitals and UMCs, particularly where this also involves international collaboration, pays off in terms of publications and impact. The TopCare hospitals used the program's resources to perform boundary work aimed at becoming an attractive and credible collaboration partner for academia. Local factors such as research history, strategic domain focus, in-house expertise, patient flows, infrastructure, and network relationships influenced collaboration dynamics within TopCare hospitals and between them and UMCs.

Keywords

Collaboration, research impact, bibliometric analysis, organizational boundary work

Introduction

Research collaboration has taken flight worldwide in recent decades (Abramo et al., 2009), as reflected by the growing number of authors listed on research papers (De Solla Price, 1963; Narin & Carpenter, 1975). Collaborative research has become the norm for many, if not most, scientific disciplines (Beaver & Rosen, 1979; Katz & Martin, 1997; Van Raan, 2004; Clark & Llorens, 2012; Bozeman et al., 2013). Several studies have found a positive relationship between collaboration and output (Lotka, 1926; De Solla Price & Beaver, 1966; Zuckerman, 1967; Morrison et al., 2003; Lee & Bozeman, 2005). Publications resulting from research collaborations tend to be cited more frequently (Beaver, 1986; Acedo et al., 2006; Wuchty & Jones, 2007; Sooryamoorthy, 2009; Gazni & Didegah, 2011) and to be of higher research quality (Beaver, 1986; Landry et al., 1996; Katz & Martin, 1997; Laband & Tollison, 2000). In particular, international collaboration can lead to more citations (Van Raan, 1998; Glänzel, 2001; Glänzel & Schubert, 2004, Sooryamoorthy, 2009; Didegah & Thelwall, 2013), although there are major differences internationally and between fields (Thelwall & Maflahi, 2020). Moreover, international collaboration is often set as an eligibility requirement for European research grants, which have become necessary as national-level resources dwindle. Funding consortia also encourage and require boundary crossings, such as research collaborations between academia and societal partners. Collaboration within public research organizations and universities further plays a crucial role in the international dissemination of knowledge (Archibugi & Coco, 2004).

In the medical domain, initiatives have been rolled out in numerous countries to encourage long-term collaboration and the exchange of knowledge and research findings. Each initiative takes a strategic approach to assembling the processes needed to support these exchanges across the boundaries of stakeholder groups. In the Netherlands, medical research has traditionally been concentrated in public academia, especially the university medical centers (UMCs). Increasingly, however, research activities are being undertaken in non-academic teaching hospitals (hereafter: non-academic hospitals), driven by their changing patterns of patient influx. In 2013, a Dutch study based on citation analysis showed that collaboration between UMCs

and non-academic hospitals leads to high-quality research (Levi et al., 2013). There was further encouragement for medical research in Dutch non-academic hospitals in 2014, when a four-year policy experiment, the TopCare program, was launched, with three such hospitals receiving additional funding from the Ministry of Health to also provide highly specialized care and undertake medical research. Funding for this combination of care and research is available for UMCs under the budgetary "academic component" of the Dutch healthcare system. Such additional funds are not available for non-academic hospitals, nor can they allocate their regular budgets to research. In the past, these hospitals managed to conduct research and provide specialized care through their own financial and time investments, or by securing occasional external research funding. The TopCare policy experiment was thus meant to find new ways of organizing and funding highly specialized care and medical research in non-academic hospitals.

Despite the increasing emphasis on research collaboration, we still know little about its impact and how it can be achieved. This study integrates two sides of research collaboration in Dutch hospitals and combines elements of quantitative and qualitative research for a broad (output and impact) and deep (boundary work to achieve collaboration) understanding of the phenomenon. We define research collaboration as collaboration between two or more organizations (at least one being a UMC or non-academic hospital) that has resulted in a co-authored (joint) scientific publication (Abramo et al., 2011). The research question is: How high is the level of collaboration in the Dutch medical research field, what is the impact of collaboration, and how are productive research collaborations achieved?

To answer these questions, we performed mixed methods research in UMCs and non-academic hospitals. To examine the impact of various collaboration models—namely, single institution, national, and international—across all eight Dutch UMCs and 28 non-academic hospitals between 2009 and 2018/2019, we conducted a bibliometric analysis of publications and citations. We additionally carried out a similar analysis for the TopCare non-academic hospitals between 2010 and 2016 to examine the effects of collaboration in the two domains funded through the program at each hospital. The latter timeframe was chosen to match the duration of the

program, 2014 to 2018. We further conducted an in-depth qualitative analysis of the organizational boundary work done by two non-academic hospitals participating in the TopCare program to initiate and enhance productive research collaborations around specialized research and care within and between hospitals on a national level. Historically, such endeavors have been predominantly reserved for UMCs. The program was therefore a unique opportunity to examine such boundary work.

Background and theory

The landscape of medical research in the Netherlands

Collaboration in medical research

The Netherlands has a three-tiered hospital system: general hospitals (including non-academic hospitals), specialized hospitals focusing on a specific medical field or patient population, and UMCs. Nowadays, there are seven UMCs, 17 specialized hospitals, and 58 general hospitals, of which 26 are non-academic (Centraal Bureau voor de Statistiek, 2024).

UMCs receive special funding (the budgetary "academic component") for research and oversee medical training programs in their region. Non-academic hospitals do not receive structural government funding for medical research and have less chance of obtaining other funding because they are not formally acknowledged as knowledge-producing organizations. Research has less priority in most of these hospitals than in UMCs. On the introduction of government policies regarding competition in healthcare and the development of quality guidelines emphasizing high-volume treatments, some non-academic hospitals began focusing on specific disease areas, in a bid to distinguish themselves from other hospitals and to perform research in and hence develop more knowledge about these priority areas. This led to a greater concentration of highly specialized care (Postma & Zuiderent-Jerak, 2017). Non-academic hospitals have also become important partners in medical research for UMCs due to their large patient volumes.

The TopCare program

To further stimulate research in non-academic hospitals, the Ministry of Health awarded three such hospitals €28.8 million in funding over a four-year period (2014-2018) to support medical research and specialized care for which they do not normally receive funding (Postma et al., 2018). It should be noted that in non-academic hospitals, the concept of highly specialized research and care applies not to the entire hospital but rather to specific departments or disease areas. This is why the TopCare non-academic hospitals have been evaluated based on specific domains. The funding recipients were two non-academic hospitals and one specialized hospital. In this article, we focus on UMCs and general non-academic hospitals and therefore excluded the specialized hospital from our analysis. Hospital #1 is the largest non-academic hospital in the Netherlands (1100 beds), even larger than some UMCs. Its fields of excellence (known as "domains") are lung and heart care. Hospital #2 is a large non-academic hospital (950 beds) that focuses on emergency care and neurology. According to the two hospitals, these four highly specialized care and research-intensive domains are comparable to high-complexity care and research in UMCs (Postma et al., 2018).

The TopCare program ran through ZonMw, the Netherlands Organization for Health Research and Development, the main funding body for health research in the Netherlands. ZonMw established a committee to assess the research proposals and complex care initiatives of the participating hospitals and to set several criteria for funding eligibility. One requirement was that participating hospitals had to collaborate with universities or UMCs on research projects and were not allowed to conduct basic research in the context of the program, as this was seen as the special province of UMCs.

Boundary work

In the qualitative part of this study, we analyze the boundary work done by actors to influence organizational boundaries as well as the practices undertaken to initiate or enhance collaboration between TopCare non-academic hospitals and academia (universities and UMCs). We refer to boundary work when actors create, shape, or disrupt organizational boundaries (Gieryn, 1983 and 1999; Abbott, 1988; Santos & Eisenhardt, 2005). In particular, boundary work involves opening a boundary for

collaboration and creating linkages with external partners (Chreim et al., 2013). In this article, we use three organizational boundary concepts—"identity," "competence," and "power"—out of four presented by Santos and Eisenhardt (2005). These concepts are concerned with fostering collaboration, whereas the fourth is concerned with "efficiency" and less relevant here. Identity involves creating a reputation for research in order to become an attractive partner while preserving identity. Competence involves creating opportunities for research, e.g., in manpower and infrastructure. Finally, power involves creating a negotiating position vis-à-vis relevant others (Santos & Eisenhardt, 2005).

Methods

The data for this study consist of different types of analysis 1) quantitative bibliometric data on the publications and citations of all eight Dutch UMCs and 28 non-academic hospitals, and 2) quantitative bibliometric data on the publications and citations in the four domains of two TopCare non-academic hospitals, qualitative (policy) document analysis, and in-depth ethnographic interviews with various actors in the Dutch TopCare program. The quantitative data collected from Dutch UMCs and non-academic hospitals were utilized to contextualize data gathered within the TopCare program. We discuss and explain the data collection and methodology in detail in the two sections.

[1] Quantitative approach: bibliometric analysis of all eight Dutch UMCs and 28 non-academic hospitals

Data collection

We performed a bibliometric analysis of the publications of 28 non-academic hospitals and eight UMCs[23] in the Netherlands between 2009 and 2018. Data

[23] The names of the UMCs and non-academic hospitals and their numbers are not up to date due to mergers in the intervening period. The database contains data on eight UMCs; today there are seven, as two UMCs in Amsterdam merged in 2018. There are 28 non-academic hospitals in the database, whereas today 27 such hospitals are members of the Association of Top Clinical Teaching Hospitals (https://www.stz.nl). To ensure data consistency, the database remains unchanged.

for the study were derived from the Center for Science and Technology Studies' (CWTS) in-house version of the Web of Science (WoS) database. The year 2009 was chosen because the address affiliations in publications are more accurately defined from this year onward. To examine trends over time, we divided the period 2009 to 2018/2019 into two blocks of four years and an additional year for citation impact measurement (2009-2012/2013 and 2014-2017/2018) (see explanation in Appendix C).

Methodology

The bibliometric analysis includes several bibliometric indicators that describe both the output and impact of the relevant research (see Table A1 in Appendix C). One of the indicators, the mean normalized citation score (MNCS), reveals the average impact of a hospital's publications compared to the average score of all other publications in that area of research. If the MNCS is higher than 1, then on average, the output of that hospital's domain is cited more often than an "average" publication in that research area.

To map the ways hospitals cooperate, we follow two lines of analysis. The first is centered around a typology of scientific activities and differentiates between: (i) single institution (SI) = all publications with only one address, and (ii) international collaboration (IC) = collaboration with at least one international partner. All other publications are grouped as (iii) national collaboration (NC) = collaboration with Dutch organizations only.

The second line is centered around geographical distance and size of collaboration. The geographical distances between each non-academic hospital and each of the eight UMCs were measured in Google Maps. The size of collaboration was measured by counting the joint publications of each non-academic hospital and the eight UMCs. Subsequently, we assessed whether the non-academic hospitals also had the most joint publications with the nearest UMC.

[2] Quantitative and qualitative approach to the two TopCare hospitals and their four domains, the "TopCare program" case study

Data collection

Quantitative approach

The quantitative approach to the TopCare program relies on a bibliometric analysis of publications within each hospital's two domains: lung and heart care in TopCare non-academic hospital #1, and trauma and neurology in TopCare non-academic hospital #2. Our bibliometric analysis focused on publications within the four selected TopCare domains between 2010 and 2016, following the same methodology described in [1]. Each domain provided an overview of its publications. The number of publications produced by the two domains at each TopCare hospital is combined in the results. Although this timeframe differs from the broader analysis of all UMCs and non-academic hospitals, comparing these two periods offers insights into the 'representative position' of the two domains of each non-academic hospital participating in the TopCare program, in terms of publications and citations.

Qualitative approach

We took a qualitative approach to analyzing the collaborative activities in the two TopCare non-academic hospitals, where each domain has its own leadership arrangements, regional demographic priorities, and history of research collaboration (cf. Waring et al., 2020). This part of the study consisted of interviews and document analysis.

Ethnographic interviews

Over the course of the four-year program, JP and/or RB conducted and recorded 90 semi-structured interviews that were then transcribed. For this study, we used repeated in-depth ethnographic interviews with the main actors in the Dutch TopCare program, which took place between 2014 and 2018. We conducted a total of 27 interviews; twenty of the interviews were with a single person, five with two persons, and two with three persons.

The interviews were held with 20 different respondents; 12 respondents were interviewed multiple times. Table 1 shows the different respondents in non-academic hospitals #1 and #2.

Table 1 Number of interviews with TopCare program actors for this study

Non-academic hospital #1 Lung and heart care	N	Number of times interviewed	Non-academic hospital #2 Emergency care and neurology	N	Number of times interviewed
Board of Directors	1	2x	Board of Directors	1	2x
Project and program leaders TopCare program	2	1: 2x 1: 3x	Project and program leaders TopCare program	3	1: 1x 2: 3x
Healthcare managers	2	2: 1x			
Researchers (2 medical specialists and 1 professor)	3	1: 1x 1: 2x 1: 3x	Researchers (2 post-docs, 3 medical specialists and 3 professors)	8	4: 1x 4: 2x
	8			12	

Document analysis

Desk research was performed for documents related to the TopCare program, see Table A2 – Details of document analysis in Appendix C.

Methodology

Quantitative approach

The bibliometric analysis of the four domains in the two TopCare non-academic hospitals follows the same methodology as described in [1].

We tested the assumption that joint publications are most frequent between a non-academic hospital and its nearest UMC. If the geographical distance between TopCare non-academic hospitals and their collaborative academic partners is described as “nearby,” then they both work within the same region.

Qualitative approach

The ethnographic interviews were audio-recorded and transcribed in full with the respondents’ permission. These transcripts were subject to close reading and coding by two authors, JP and JO, to identify key themes derived from

the theory (Santos & Eisenhardt, 2005) (see Table A3 in Appendix C). These were then discussed and debated with the wider research team with the goal of developing a critical interpretation of the boundary work done to initiate or enhance research collaboration (Waring et al., 2020). The processed interview data were submitted to the respondents for member check. All respondents gave permission to use the data for this study, including the specific quotes. In the Netherlands, this research requires no ethical approval.

Triangulating the results of the document analysis and the interviews enables us to identify different overarching themes within each boundary concept (identity, competence and power). These themes were utilized as a framework for structuring individual paragraphs, which we explain in greater detail in Table 4 in the Results.

Results

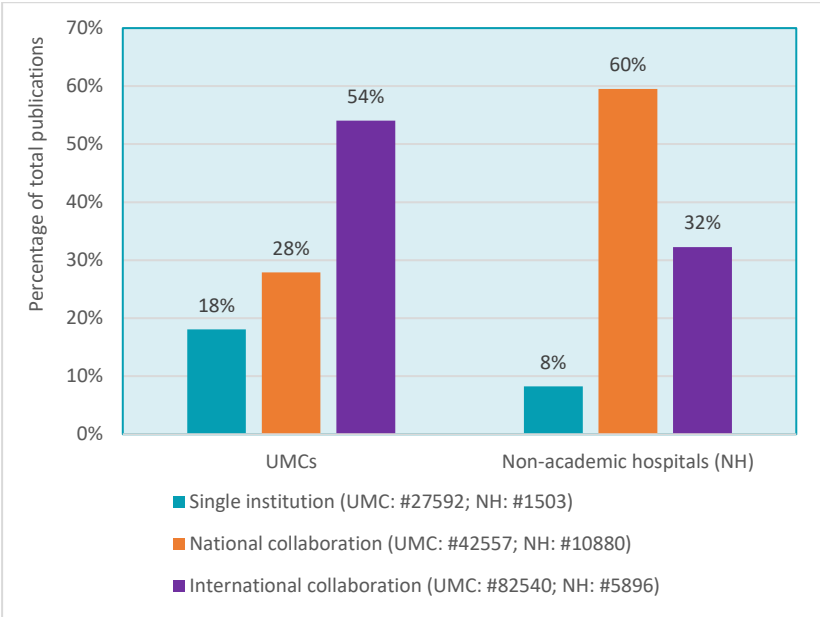
Bibliometric analysis of all Dutch UMCs and non-academic hospitals

This section reports the results of the quantitative bibliometric analysis of the output, trends, and impact of collaboration between all UMCs and non-academic hospitals from 2009 to 2018/2019. It provides a broad picture of the output – in terms of research publications – of both existing and ongoing collaborations between all UMCs and non-academic hospitals within the specified timeframe. It furthermore describes the analysis results concerning the relationship between collaboration and the geographical distance between two collaborating hospitals.

Output: distribution of the types of collaboration for UMCs and non-academic hospitals from 2009 to 2018/2019

The first step in understanding the degree of collaboration between hospitals is to measure the research output by number of publications. The total number of publications between 2009 and 2018 is shown in Table A4 (see Appendix C) and Figure 1.

Figure 1 Types of collaboration for UMCs and non-academic hospitals from 2009 to 2018/2019



#: Total number of publications
Percentage of total (100%) accounted for by single institution, national collaboration, international collaboration

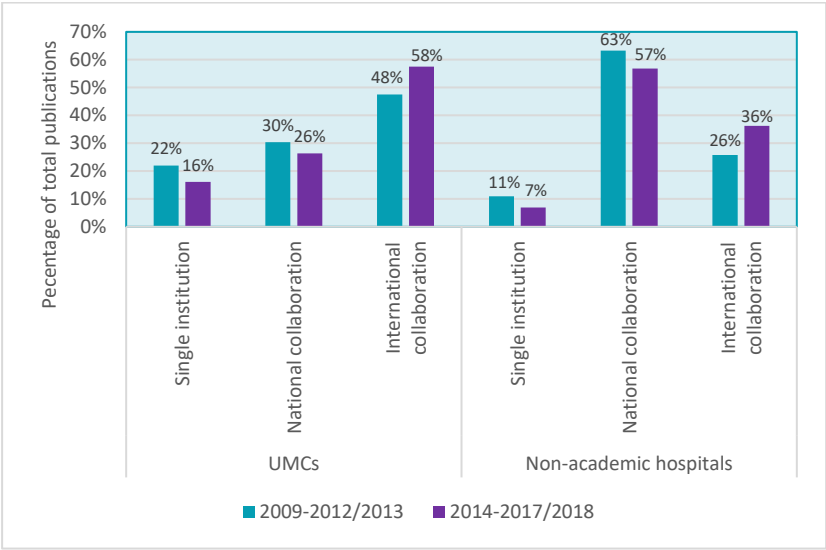
The majority of these publications (89%) are affiliated with UMCs. UMCs, in particular, tend to have a relatively higher proportion of single institution publications and are more engaged in international collaboration. This pattern may be indicative of UMCs' enhanced access to research grants and EU subsidies, as well as their active involvement in international consortia.

Collaboration between UMCs and non-academic hospitals appears to be more prevalent and impactful for non-academic hospitals than for UMCs: 70% of all publications originating from a non-academic hospital were the result of joint efforts between a UMC and a non-academic hospital, whereas only 8% of all UMC publications were produced in collaboration with a non-academic hospital (see Table A4 in Appendix C).

Trend analysis of collaboration in relative number of publications

Table A5 (see Appendix C) and Figure 2 show the relative number of publications of all eight UMCs and all 28 non-academic hospitals in the two periods: 2009-2012/2013 and 2014-2017/2018. For both UMCs and non-academic hospitals, international collaboration accounted for a relatively larger share of publications in recent years.

Figure 2 Type of research collaboration for UMCs and non-academic hospitals over time



Percentage of total (100%) accounted for by single institution, national collaboration, international collaboration in each period

Analysis of relationship between distance and collaboration

As the non-academic hospitals often collaborate with UMCs, it is interesting to analyze these collaborations geographically (distance). The assumption is that geographical proximity matters, with the most-frequent joint publications being between a non-academic hospital and the nearest UMC.

Figure 3 Collaboration with nearest UMC from 2009 to 2018

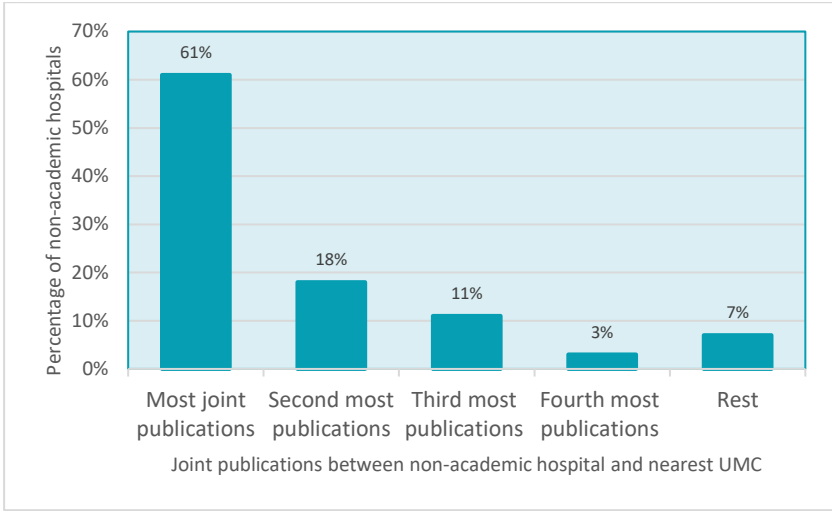


Figure 3 shows that 61% (17 out of 28) of the non-academic hospitals collaborate most frequently with the nearest UMCs. Geographical proximity is thus an important but not the only determining factor in collaboration.

Impact of collaboration on bibliometric output of UMCs and non-academic hospitals

The mean normalized citation scores (MNCS) shown in Table 2 cover all eight UMCs and 28 non-academic hospitals.

Table 2 MNCS

	2009-2018/2019				2009-2012/2013			
	UMCs	#	Non-academic hospitals	#	UMCs	#	Non-academic hospitals	#
SI	1.27	27592	0.90	1503	1.32	11204	0.93	704
NC	1.20	42557	1.22	10880	1.28	15468	1.35	4060
IC	2.05	82450	2.24	5896	2.08	24133	2.16	1656

If the MNCS is higher (or lower) than 1, then on average, the output of the domain is cited more often (or less often) than an "average" publication in the research area in which the domain is active.
SI: single institution, NC: national collaboration, IC: international collaboration
#: Total number of publications

Table 2 Continued - MNCS

	2014-2017/2018			
	UMCs	#	Non-academic hospitals	#
SI	1.24	11085	0.85	559
NC	1.17	18087	1.17	4556
IC	2.01	39493	2.32	2908

The MNCS in Table 2 and the mean normalized journal scores (MNJS) in Table A6 (see Appendix C) show similar patterns. The impact score for both UMCs and non-academic hospitals is greatest for international collaboration. Non-academic hospitals' single institution publications score lower than the global average, which was defined as 1.

In sum, quantitative analysis exposes two trends. The first is growth in international collaboration for all UMCs and non-academic hospitals over time, also revealing that collaboration leads to higher MNCS impact scores. Second, geographical proximity between UMCs and non-academic hospitals is an important but not the only determining factor in collaboration. This is the context in which the TopCare program operated in 2014-2018.

"TopCare program" case study

This section presents the results of our analysis of the collaboration networks of the two TopCare non-academic hospitals, consisting of: 1) quantitative bibliometric analysis of the output and impact of these networks between 2010 and 2016, along with the geographical distance to their academic partners, and 2) qualitative ethnographic interviews to identify the boundary work conducted by these hospitals.

Bibliometric analysis of the two TopCare non-academic hospitals' international and national collaboration networks across four domains

The results of the bibliometric analysis indicate the representative positions of the two domains within each TopCare non-academic hospital. Between 2010 and 2016, these hospitals generated a higher number of single institution publications compared to the average of all non-academic

hospitals. Percentage-wise, their output resembled that of the UMCs, underscoring their leading positions in their respective domains. The percentage of publications based on national collaboration in the domains of TopCare hospital #2 is comparable to that of non-academic hospitals overall, while there is more international collaboration in the domains of TopCare hospital #1 than at non-academic hospitals overall (see Figure A1, Appendix C and Figure 1 above). The impact of the research is above the global average and the publications have a higher average impact when there is collaboration with international partners; this is true across all four domains (see Table A7 in Appendix C).

In terms of geographical distance, only the neurology domain of TopCare hospital #2 collaborates with an academic partner within the same region. All other domains collaborate with partners outside the region, a striking difference from the geographical results shown in Figure 3.

Ethnographic analysis

This section reviews the results of our ethnographic analysis of the two TopCare hospitals from 2014 to 2018. To analyze the boundary work these hospitals performed to initiate and/or enhance productive research collaborations, we use the framework suggested by Santos and Eisenhardt (2005) for examining organizational boundary work through the concepts of identity, competence, and power. Table 3 provides a description of each boundary and how these concepts are defined in our case study based on the overarching themes in the document analysis and the interviews.

Table 3 Description of each boundary to case study specifications

	Description of each boundary (based on Siaw & Sarpong, 2021; Velter et al., 2021)	Case study specifications
Boundary of identity	Maintain coherence between the hospital's dominant mindset of "who we are" and its organizational activities.	[a] Enhancing the hospitals' value proposition
Boundary of competence	Maximize the value of a hospital's resource portfolio by matching resources with opportunities of its collaborative partners.	[a] Enhancing research infrastructures [b] Finding alignments within hospitals and research networks
Boundary of power	Maximize strategic control over crucial relationships, and increase the hospital's power in a particular domain.	[a] Enhancing the relationship with or finding and mobilizing strategic academic partners [b] Aligning with the board of directors and administrators of the TopCare hospitals

Identity: enhancing hospitals' value proposition

In the TopCare program, the non-academic hospitals used their unique history and expertise to create a joint research focus in a domain and to enhance their positions and influence their collaboration with UMCs and universities.

A manager in hospital #1's lung domain explained the work being done from a historical perspective, emphasizing not only the innovative history of the hospital, but also its central position in patient care:

> "The first-ever lung lavage, lung transplant and angioplasty were performed in this hospital. Nationally, this hospital has always, and we're talking about 50-60 years ago now, been at the forefront, and has always invested in this line of research and care. So that is truly institutionally built, there is just that history and you can't just copy that. And we have the numbers: for interstitial lung diseases, we have 2000 patients in our practice and receive 600 new patients per year." (interview with manager at hospital #1 in 2018)

To explain why patient care and research into rare interstitial lung diseases is centered in hospital #1 as a strategic domain focus, a leading international pulmonary physician – a "boundary spanner" (see below) – pointed to the importance of building team expertise and creating facilities:

> "I lead that care program for interstitial lung diseases and preside over the related research. I've often been asked: you're a professor, so why don't you go to a UMC, couldn't you do much more there? But the care was developed here [in this hospital]. The expertise needed to recognize interstitial lung diseases depends not only on me but also on the radiologist and pathologist; together we have a team that can do this. We have created facilities that no other hospital has for these diseases. If I leave to do the same work in a UMC, I'd have to start over and I'd be going back 30 years." (interview with pulmonary physician at hospital #1 in 2014)

The doctors working in this hospital's lung and heart domains finance the working hours they put into research themselves. "*This fits in with the spirit of a top clinical hospital and the entrepreneurial character of our hospital.*" (interview with project leader at hospital #1 in 2018)

Hospital #2, the result of a merger in 2016, struggled to find its strategic focus. A surgical oncologist at this hospital clarified one of the disadvantages of the merger: *"People are [still] busy dealing with the money and positions, and the gaze is turned inward, the primary processes. So clinical research is very low on the agenda."* She continued by saying that a small project team acting on behalf of the hospital's board of directors (BoD) was seeking the best-fit profile for the program, which had raised some opposition in departments excluded from the chosen strategic focus. As a consequence, the hospital had begun to showcase its highly specialized care in the field of neurosurgical treatments. It had a long history and was the first to use a Gamma Knife device for treating brain tumors. The experts in this domain could thus act as authorities and became a national center of expertise. Their strategic partner was a nearby UMC, and they treated relevant patients from other hospitals in their region.

To generate impact, research priorities in a domain are aligned with the focus of the hospital. A member of the BoD of hospital #2 stressed the urgency of *"specializing or focusing on a particular area of care"* and emphasized that the TopCare budget was being utilized to create a joint focus within a domain. The resulting collective identity mobilized internal affairs and was recognized as valuable by third parties. An important reason for joining the TopCare program for both hospitals was to be able to position themselves strategically as attractive and credible research partners:

> "The focus is on the domains of neurology and trauma because we think as a non-academic hospital we have something extra to offer: the very close relationship between patient care and research, because we have a larger number of patients of this type here than the universities." (interview with care manager at hospital #2 in 2013)

In short, the boundary of identity requires a closer alignment between these hospitals' research activities and their strategic objectives and organizational mindset, and demands that they also showcase their staff's expertise. The TopCare program offered opportunities to transform and consolidate their identity by enhancing their value proposition, i.e., their unique history, strategic domain focus, expertise, and number of patients.

Competence: enhancing research infrastructures

All domains in the TopCare program chose to utilize the TopCare funding to invest in their research infrastructure, and to build research networks in order to share and learn. A research infrastructure consists of all the organizational, human, material, and technological facilities needed for specialist care and research (Postma et al., 2018).

The TopCare data show that funding is essential for generating research impact. A manager at hospital #1 described its current financial circumstances:

> "A lot of research and much of the care is currently not funded, it is actually paid for mostly by the hospital... We have had massive budgetary adjustments the past two or three years. ...It is increasingly difficult to finance these kinds of activities within your own operation." (interview with manager at hospital #1 in 2018)

The TopCare funding was used to enhance the material infrastructure in hospital #1's heart domain:

> "A number of things in healthcare are really terribly expensive, and there is simply no financing at all for them. …Cardiac devices, for example. We are constantly trying things out, but there's no compensation for it." (interview with project leader at hospital #1 in 2018)

Hospital #1 had a long-standing and firm relationship with a UMC in the lung domain, giving it a solid material infrastructure. For example, there were spaces where researchers, especially PhD students, could meet, collaborate, and share knowledge (Postma et al., 2018). Another essential part of the material infrastructure for the lung domain was the biobank, as highlighted by a leading international pulmonary physician:

> "Our board of directors made funds available through the innovation fund to start up a biobank, but developing it and keeping it afloat has now been made possible thanks to the TopCare funding. It's a gift from heaven! It will allow for further expansion and we can now seek international cooperation." (interview with pulmonary physician at hospital #1 in 2014)

Notably, the program allowed both non-academic hospitals to digitize their infrastructure, e.g., with clinical registration and data management systems. According to an orthopedic surgeon at hospital #2, "Logistics have been created, which can very easily be applied to other areas. By purchasing a data system, everyone can record data in a similar way."

Besides investing in data infrastructure, the human dimension was another crucial factor in the research infrastructure. Instead of working on research "at night," it became embedded in physicians' working hours. All domains indicated the importance of having researchers, statisticians, and data management expertise available to ensure and enhance the quality of research, and both hospitals invested in research staffing.

After losing many research-minded traumatologists to academia, hospital #2 decided to invest in dedicated researchers to form an intermediate layer of fulltime senior researchers linked to clinicians within the two domains.

> "I personally think this is the most important layer in a hospital, with both a doctor and a senior researcher supervising students and PhD candidates. Clinicians ask practical questions and researchers ask a lot of theoretical questions. Both perspectives are needed to change practices. I have also learned that it takes a few years before the two can understand each other's language." (interview with neurosurgeon at hospital #2 in 2018)

Competence: finding alignments within hospitals and research networks

The program offered the hospitals opportunities to structure internal forms of collaboration and build a knowledge base within a domain. For example, hospital #1 organized educational sessions with all PhD students in the heart domain.

> "Having more researchers working in our hospital has given the whole research culture a boost, as well as the fact that they are producing more publications and dissertations." (interview with cardiologist at hospital #1 in 2018)

Hospital #2 also encouraged cross-domain learning by organizing meetings between the neurology and trauma domains.

> "You know, you may not be able to do much together content-wise, but you can learn a lot from each other in terms of the obstacles you face" (interview with project manager at hospital #2 in 2016)

At the beginning there was resistance to participating in the program.

> “It was doom and gloom; without more support, groups refused to join. That kind of discussion. So the financial details have been important in terms of willingness to participate." (interview with surgical oncologist at hospital #2 in 2018)

Another obstacle was local approval for multicenter studies, which led to considerable delay (interview with psychologist at hospital #2 in 2018). Overall, the TopCare program created a flywheel effect for other domains that proved essential for internal collaborations (interview with surgical oncologist at hospital #2 in 2018).

In hospital #1, collaboration between the heart and lung domains grew closer.

> “Divisions between the different disciplines are much less pronounced in our hospital than in UMCs. So it’s much easier to work together. We’d already collaborated closely on lung diseases, and this has improved during the program.” (interview with cardiologist at hospital #1 in 2016)

At the network level, the TopCare data show that most researchers participated in national networks. For example, the neurology domain in hospital #2 had established a network of 16 non-academic hospitals. Limited funding prevented researchers at non-academic hospitals from attending many international seminars and they had more trouble building their international networks. One exception concerned the researchers in the lung domain of hospital #1, who expanded their international network by organizing an international seminar during the TopCare program and by contributing to other national and international seminars.

Each TopCare domain provided highly specialized care and wanted to become a center of expertise. However, a hospital can only provide highly specialized care if research is conducted to determine the best treatment strategies. The data show how the two are interwoven.

> "For example, a PhD student has sought to collaborate with a UMC on a specific aorta subject in which we have greater expertise and more volume in terms of patients than UMCs. Based on this link with this UMC, a different policy was drawn up and also implemented immediately in all kinds of other UMCs." (interview with cardiologist at hospital #1 in 2018)

Often, a leading scientist who is the driving force behind a domain in a hospital is a "boundary spanner", a person in a unique position to bridge organizational boundaries and foster research collaboration by "enabling exchange between production and use of knowledge" (Bednarek et al., 2018, p. 1176; Neal et al., 2022). For example, the leading pulmonary physician in hospital #1 is a boundary spanner, who has done a huge amount of work to enhance collaboration. With interstitial lung disease care being concentrated here, this professor can offer fellowships and stimulate virtual knowledge-sharing by video conferencing for "second-opinion" consultations. The TopCare funding was used to finance this. The network is successful at a non-academic level.

> "These consultations are with colleagues in other hospitals and they avoid patients having to be referred." (interview with project leader at hospital #1 in 2018)

> "Our network now [in 2018] consists of more than 14 hospitals, which we call every week to discuss patients with an interstitial lung disease. …UMCs participate indirectly in this network. For example, the north has a specific center for this disease in a non-academic hospital and a nearby UMC refers patients to this center, who are then discussed in our network." (interview with pulmonary physician at hospital #1 in 2018)

This physician also noted that the network was still growing; other colleagues from non-academic hospitals wanted to join it.

> *"*Yesterday, colleagues from XX and XX were here. And they all said, 'I've never learned so much about interstitial lung diseases.' We're imparting enormous amounts of expertise." (interview with pulmonary physician at hospital #1 in 2018)

In sum, focusing on the boundary of competence, the TopCare hospitals created and mobilized resources to invest in their research infrastructure. In every domain, this infrastructure was used to strengthen the relationship between research, care, and education, and to build and enhance internal and external research networks in order to share and learn.

Power: enhancing the relationship with or finding and mobilizing strategic academic partners

For TopCare non-academic hospitals, the boundary of power is concerned with creating the right sphere of influence, meaning BoDs and administrators attempt to find and mobilize new strategic partners and build mutual relationships with various stakeholders at different levels.

A project leader at hospital #2 emphasized that the additional resources of the TopCare program created an opportunity for the non-academic hospitals *"to show our collaborative partners that we're a valuable partner."* For once, the tables were turned:

> "We've always had a good relationship with one UMC; they always used the data from our surgeries. But it's nice that we can finally ask them whether they want to join us. That makes it a little more equal, and we can be a clinical partner." (interview with neurosurgeon at hospital #2 in 2018)

One of the requirements in each domain when applying to ZonMw for funding was alignment with academia in a research and innovation network. Collaboration often appeared more difficult at the administrative level when the academic partners worked in the same field of expertise and tended to be more successful when the partners focused on different fields, where their

interests did not conflict. According to a board member at hospital #2 who played a crucial role in a partnership agreement, a conscious decision was taken beforehand to seek partners beyond the medical domain as well.

> "There may be conflict with other groups within the walls of a UMC and I don't see that as promising. You have to work together and we aren't in a real position to do so." (interview with board member at hospital #2 in 2018)

Just before the end of the program, it was announced that this hospital had concluded a partnership agreement with a university to broaden their joint research program alongside neurology and trauma. An important prerequisite was that both organizations invest one million euros in the partnership. The board member revealed that the relationship with this university had in fact existed for some time:

> "So we went and talked to the university and they became interested. Then the top level was reorganized and replaced and we had to start from scratch again. That took a lot of time. Our goals were to awaken the enthusiasm of the board and at least three deans, otherwise it would be a very isolated matter. And we succeeded. Last week we had a matchmaking meeting at the university and there were about 50 pitches showing how we could be of value to each other." (interview with board member at hospital #2 in 2018)

Looking back, he defined the conditions for a successful collaboration with academia:

> "In terms of substance, the two sides have to be going in the same direction and complement each other, for example in expertise, techniques, and/or facilities. And what is really important is that people know each other and are willing to meet each other…and there must be appreciation." (interview with board member at hospital #2 in 2018)

The trauma domain in hospital #2 wanted to become a trauma research center in its region, and after investing in its research infrastructure, it found a new strategic academic partner:

> "We have also found new partners, for example, the Social Health Care Department of a UMC [name]. And that really has become a strong partnership; the intent was there for years, but we had no money." (interview with epidemiologist at hospital #2 in 2018)

The neurology domain at this hospital worked to form a network with a university of technology and a university social science department.

> "Officially, our hospital can't serve as a co-applicant for funding and that is frustrating. However, I am pleased to show that we are contributing to innovation." (interview with neurosurgeon at hospital #2 in 2018)

A board member at this hospital reflected on the qualities needed for research and concluded: *"The neuro group has more of those intrinsic qualities than the trauma group. …I think the trauma group is actually at a crossroads and will think twice about whether they can attract capacity to develop the research side or fall back to a very basic level."*

In hospital #1, administrators rejected a proposal to collaborate with the nearest UMC submitted by medical specialists in the heart domain. Past conflicts and unsuccessful ventures still influenced the present, even though the individuals involved had already left.

A further factor was raised by a manager at hospital #1, who reflected on the importance of obtaining a professorship in the heart domain:

> "If we can, even on the basis of any kind of appointment, obtain a professorship from the heart center, then yes, that helps! …I think it just helps throughout the whole operation, politically speaking, as extra confirmation, extra legitimization for that status." (interview with manager at hospital #1 in 2016)

Eventually, hospital #1 managed to find alignment with a UMC in another region during the program and a medical specialist from the hospital became a professor by special appointment.

> "This UMC showed the greatest determination, actually, while we could have chosen to collaborate with the nearest UMC [but we didn't]. And there was actually also a real click between both the administrators and the specialists." (interview with manager at hospital #1 in 2018)

Additionally, the TopCare data show that while there may be close alignment with the nearest UMC, collaboration is not limited to this and proximity can sometimes even be detrimental (e.g. in some cases hospitals compete for patients). As research and care in the TopCare hospitals' domains became more specialized, they required the specific expertise of UMCs in other regions.

One critical dependency in the collaboration between a university or UMC and a non-academic hospital is the distribution of dissertation premiums, valued at about €100k per successful PhD track. Currently, after completion of a dissertation, the premium goes entirely to the university or UMC, even when much of the candidate's research and supervision takes place in a non-academic hospital (Postma et al., 2018). This structural difference makes collaboration less financially valuable to non-academic hospitals. For example, the leading pulmonary physician in hospital #1 is a professor who is affiliated with both a UMC and non-academic hospital, a boundary spanner who works across organizational boundaries, is successful in research, and bears responsibility for a significant proportion of the research output in the lung domain and in the collaboration with other organizations. Moreover, he does most of the PhD supervision and his students do their work in hospital #1. Despite all this work, the dissertation premium goes to the UMC. Although efforts have been made to change this, certain institutional structures are so strongly embedded that it is difficult to open the organizational boundary.

Power: aligning with the BoDs and administrators of the TopCare non-academic hospitals

During our research, we observed how the BoDs and administrators of the two TopCare hospitals discussed the progress of the program and worked together to learn from each other.

> "We can learn a lot from hospital #1 regarding the organization of our research, we think. That has been very inspiring. …On the other hand, the focus has been very centered on getting the domain and project requests funded at all." (interview with care manager at hospital #2 in 2013)

The BoDs opted for an approach aimed at building mutual trust and understanding. As a result, their alliance became more intensive during the program. By the time the program's final report was released, both BoDs were leveraging their power to influence ZonMw's next step: the follow-up to TopCare. They had a targeted plan for their lobbying. For example, after mutual coordination, the BoD of each hospital sent a letter to the Ministry of Health sketching their vision for the future.

In summary, for the TopCare hospitals, the boundary of power centered on finding alignment with strategic academic partners and the other BoDs and administrators in the TopCare program. Moreover, ties with strategic partners were important for extending the organization's sphere of influence (Santos & Eisenhardt, 2005) in building and enhancing productive research collaborations. These hospitals recognized that they could not dismantle the existing structure of research funding and they therefore committed themselves to trying to extend the TopCare program. Table 4 summarizes the opportunities and challenges within the three boundary concepts.

Table 4 Opportunities and challenges within the three boundary concepts

Section of analysis	Opportunities	Challenges
Boundary of identity	-Enhance value proposition by integrating unique history, strategic focus, expertise, and patient volume	-Fund doctors' research hours -Manage disruptions from hospital mergers
Boundary of competence	Strengthen research-care-education synergy: -Invest in research infrastructure, enhance materials, expand human resources and digitalize -Build and enrich both internal/external research networks for knowledge-sharing and learning	-Allocate research infrastructure resources -Stakeholder resistance -Limited funding hampers international networking
Boundary of power	-Establish conducive environment for partnerships: ensure equitable financial contributions or acquire professorships -Achieve success with diverse partners: minimize conflicts and expand beyond medicine -Cultivate relationships with BoDs and administrators -Consolidate authority to influence ZonMw's TopCare follow-up	-Insufficient funding for doctors' research time -Co-applicant limitations for funding -Past conflicts influence partnerships -Complicating factor: dissertation rewards to universities/UMCs

Discussion

In our study, we used a mixed methods research design to explore research collaborations by focusing on the research output and impact of UMCs and non-academic hospitals in the Netherlands and by zeroing in on the boundary work of two Dutch non-academic hospitals for achieving collaboration.

Our bibliometric analysis shows that collaboration matters, especially for non-academic hospitals. Access to research grants, EU funding, and international collaborations is harder for non-academic hospitals, and they need to collaborate with UMCs to generate research impact, assessed by means of MNCS impact scores. Conversely, non-academic hospitals are important for UMCs because they have a larger volume of patients. When UMCs and non-academic hospitals collaborate, their impact scores are higher.

Impact scores are, moreover, higher for international collaborative publications across all types of hospital and all periods. More in-depth research is needed into why collaboration increases impact.

Bibliometric analysis of the domains of the two TopCare non-academic hospitals underscores their leading role in these domains. Upon receiving TopCare funding, the hospitals had to engage in various forms of boundary work to meet the requirement mandated by ZonMw of establishing a research collaboration with academia. They used the additional program resources to invest (Santos & Eisenhardt, 2005) in opening a boundary for research collaboration with academic partners.

Identity work involves creating an image of the organizational unit that legitimizes its research and care status in line with the dominant mindset of the organization. In practice, the relevant unit needs to establish a distinctive history and domain focus that aligns with the organizational strategy of the hospital, in-house expertise and patient flow. This requires coordination work with the BoD. However, not all domains have been successful in creating such an identity. It proved much more difficult for the trauma domain, for example, because their research is not as highly specialized as and more fragmented than the other domains.

Competence work focuses on organizational (a well-functioning science support unit), technological (registration systems), and material (floor space or biobank) infrastructure, depending on individual requirements. Additionally, tremendous efforts go into the human dimension of infrastructure, as TopCare hospitals consider research staff and making time available for doctors to be important conditions for building structurally supportive research programs. In a previous study, we highlighted that collaboration between all non-academic hospitals within the Association of Top Clinical Teaching Hospitals (STZ) is essential for strengthening their research infrastructure (Van Oijen et al., 2020), and can also be seen as a matter of efficiency (Santos & Eisenhardt, 2005). Moreover, in each TopCare hospital, competence work served to bring domains together to facilitate

shared learning. Knowledge-sharing across departments or communities is an example of opening boundaries to facilitate integration, convergence, or enrichment of points of view (Carlile, 2004; Chreim et al., 2013; Orlikowski, 2020).

Professors with double affiliations can act as boundary spanners. They play a significant role as experts in a domain by creating its distinctive character and they surmount borders and break down barriers through their network relationships with other hospitals. Additionally, these persons are responsible for a significant share of the research output in their domain and conduct research with worldwide impact in collaboration with other organizations. Their boundary work must be recognized as essential because they bring usable knowledge to the table, create opportunities for improved relationships across disciplines, enhance communication between stakeholders, and facilitate more productive research collaborations (cf. Goodrich et al., 2020).

The TopCare hospitals do much less work in the power dimension because the domains in which they operate are adjacent to those of academia. Our study shows that more successful, productive research collaborations are created when the hospital's academic partner works in a complementary but not identical field. Only in one case, the heart domain, did collaboration succeed in an identical field, but that was because the academic partner was located outside of the hospital's region and was therefore not a competitor. According to Joo et al. (2019), a potential partner's suitability is determined not only by complementarity, their unique contribution to research collaboration in terms of expertise, skills, knowledge, contexts, or resources, but also by compatibility and capacity. Partner compatibility involves alignment in vision, commitment, trust, culture, values, norms, and working styles, which facilitate rapport-building and cross-institutional collaboration (Joo et al., 2019). TopCare data indicate that research collaborations should be managed to ensure all partners can operate as equals (McDonald et al., 2012). Partner capacity refers to the ability to provide timely resources (e.g. expertise, skills, or knowledge) for projects, as well as leadership commit-

ment, community engagement, and institutional support for long-term, mission-driven goals, such as the joint research program in neurology and trauma at hospital #2 and a university.

These three qualitative criteria - partner compatibility, complementarity, and capacity - are aspects of power dynamics that influence strategic decisions about recruiting research partners. Generally, power dynamics shape a hospital's strategic choices regarding whether to collaborate, with whom to partner, and the extent of the research collaboration (Harrington et al., 1998). Future research should examine these power dynamics in a more integrated manner to unlock the full potential of collaboration (Joo et al., 2019).

It was possible to unravel how non-academic hospitals participating in the TopCare program engaged in research collaborations with academia. As the program did not interfere with the existing care, research, and financing structures within the UMCs, it allowed TopCare non-academic hospitals to also combine top clinical care and research. The boundary concepts allow us to observe a dual dynamic in the collaboration: the opening of boundaries while simultaneously maintaining certain limits. Opening boundaries refers to facilitating collaboration through activities related to identity and competence, while maintaining them involves the power balance. The temporary program did not disrupt the existing power balance associated with the budgetary “academic component” and the dissertation premiums that accrue to academia. Overall, then, the power dimension may well be the primary factor that made it impossible for the TopCare non-academic hospitals to attain their ultimate goal: secure a consistent form of funding for their research and top clinical care. Instead, the national authorities introduced a new, temporary funding program for non-academic hospitals, and preserved the status quo favoring academia.

A key finding is that if a hospital is successful in establishing coherence between the different forms of boundary work, it can create productive research collaborations and generate research impact. The TopCare hospitals performed boundary work to strengthen their research infrastructure (competence) and their research status (identity) and create a favorable negotiating position opposite academia (power). For example, choosing the

lung domain as the hospital's strategic focus (identity) and establishing a database as a fundamental source of information for research by a boundary spanner (competence) generated sufficient power to make the hospital a key player in this field and a much-respected collaboration partner, nationally and internationally. However, some restrictions remained in place, such as the national lung research network consisting only of non-academic hospitals, with UMCs participating only indirectly.

Another key finding is that possessing a substantial budget is not in itself enough to ensure successful research collaboration. It is clear from this study that extensive boundary work is also needed to facilitate research collaboration. Given the absence of structural funding, the TopCare non-academic hospitals were under pressure to deliver results during the program, making research collaboration even more crucial for them than for the UMCs in this context. Additionally, because highly specialized care and research at the TopCare non-academic hospitals required unique expertise, they had a growing need for collaboration at the national level. Contrary to assumptions and the findings of our analysis of UMCs and non-academic hospitals overall, their collaborative partners were not predominantly located at the nearest UMC.

Does our study align with the literature and support the results of similar initiatives, such as the establishment of Collaborations for Leadership in Applied Health Research and Care (CLAHRC), a regional multi-agency research network of universities and local NHS organizations focused on improving patient outcomes in England by conducting and utilizing applied health research (Soper et al., 2015)? And what does it contribute to previous research?

While differences exist between the National Health Service (NHS) and the healthcare system in the Netherlands, there are also noteworthy parallels that render a comparison possible. These include encouraging networks to boost research productivity, fostering collaboration within a competitive system, and funding research that is relevant to public health priorities. Moreover, building upon the findings of CLAHRC regarding boundary work within a competitive system, and developing and funding research that is

relevant to patient needs and public health priorities, there are further parallels, such as creating strong local research infrastructures and local networks (Soper et al., 2015), and using influential and skilled boundary spanners (Lockett, 2014; Soper et al., 2015). In addition, we found that research history, strategic domain focus, in-house expertise, patient flows, and network relationships pre-conditioned the TopCare hospitals' collaboration with academia. Our results further show that for non-academic hospitals seeking to create productive research collaborations, it is essential to work in complementary fields and to establish a coherence between identity, competence, and power.

Our findings indicate that after opening a boundary with academia, the focus of the TopCare hospitals was on searching for mutual engagement. These hospitals tried to clarify their added value by creating boundaries to distinguish themselves from UMCs, and attempted to extend the TopCare program without it overlapping with the budgetary "academic component," so that it posed no threat to the UMCs. Boundary-crossing involves a two-way interaction of mutual engagement and commitment to change in practices (Engeström, 2003). It is likely that the program did not last long enough to instigate changes in practices, as it can take time to develop mutual understanding and foster trusting relationships (Gezondheidsraad, 2016).

Based on the CLAHRC results and our research findings, the trend toward regionalization in the Netherlands (Van der Woerd, 2024) and a new leading and coordinating role for UMCs in this research landscape (Gezondheidsraad; 2016, Iping et al., 2022) can only be successful if boundary work is conducted, allowing research-minded non-academic hospitals to:

- build a "collaborative identity" (Kislov et al., 2011; Lockett et al., 2014; Rycroft-Malone et al., 2015) over time with their academic partners (identity)
- establish added value in their research infrastructures compared to that of their academic partners (competence)
- create solid networks for learning and sharing knowledge (Harvey et al., 2011; Rycroft-Malone et al., 2015) with their academic partners (competence)

- mobilize boundary spanners to bridge disciplinary and professional boundaries in research, teaching, and practice (Currie et al., 2013; Lockett, 2014; Rycroft-Malone et al., 2015; Soper et al., 2015) and publish articles in collaboration with academic partners with high research impact (competence)
- find the inspiration and confidence to increase their co-dependence in order to, for example, gain benefits from interacting with different partners in the field (Santos & Eisenhardt, 2005) (power), and
- create long-term collaborations with academia across sectors over time, as well as within sectors; this requires iterative and continual engagement between clinicians, academics, managers, practitioners, and patients (power) (Soper et al., 2015; Gezondheidsraad, 2016).

It is conceivable that the evaluation of the follow-up study to the TopCare program, which will extend to 2025, could unravel these next steps.

Our results demonstrate that collaboration in research is important and should be encouraged. However, the current methods used to assess researchers underestimate this importance. Reward systems and metrics focus on the performance of individual researchers and may even discourage the development of medical research networks and collaboration (Hurley, 2011; Gezondheidsraad, 2016). There is ongoing debate about and rising criticism of the dominance of scientific impact scores as a measure of the performance of health researchers and research organizations (DORA, n.d.). Other forms of impact, such as the societal impact of medical research, are becoming more important, and different metrics are being developed. Research collaboration among individuals and organizations should be incentivized and rewarded, and should also be embedded in performance assessment and the core competences of all actors involved (O'Leary & Gerard, 2012). New ways of rewarding research collaboration within organizations should therefore be explored.

Limitations

This study is limited, both geographically and institutionally, to the Netherlands, and factors other than national and international research collaborations may explain the increase in research output and impact. For example, the research articles in our sample have not been analyzed on substantive aspects such as methodology and funding. A bias may therefore have been introduced. Furthermore, the research output and impact of the TopCare non-academic hospitals that we measured was limited to the four-year program period. A further limitation was the use of these hospitals' research output as a measure of the influence of the TopCare program, as we were interested not only in the short-term effects (publications), but also in the long-term ones (on the work conducted to build research infrastructures). Moreover, the focus in the qualitative material concerning the TopCare program was on the two TopCare non-academic hospitals and, more specifically, on their national rather than their international collaborations.

Conclusions

Research collaboration between non-academic hospitals and academia in the Netherlands pays off in terms of publications and impact. For the publication of scientific articles, collaboration between UMCs and non-academic hospitals appears to be more prevalent and impactful for non-academic hospitals than for UMCs. When UMCs and non-academic hospitals collaborate, their impact scores tend to be higher. More research is needed into why collaboration leads to more impact.

Non-academic hospitals showed a higher rate of collaboration with the nearest UMC, whereas collaborative partners of TopCare hospitals were not predominantly located at the nearest UMC. TopCare hospitals prioritized expertise over geographical proximity as a predicator of their collaborative efforts, particularly as research and care in their domains became more specialized.

Drawing on the additional resources of the TopCare program, participating non-academic hospitals invested significantly in boundary work to open boundaries for research collaboration with academic partners and,

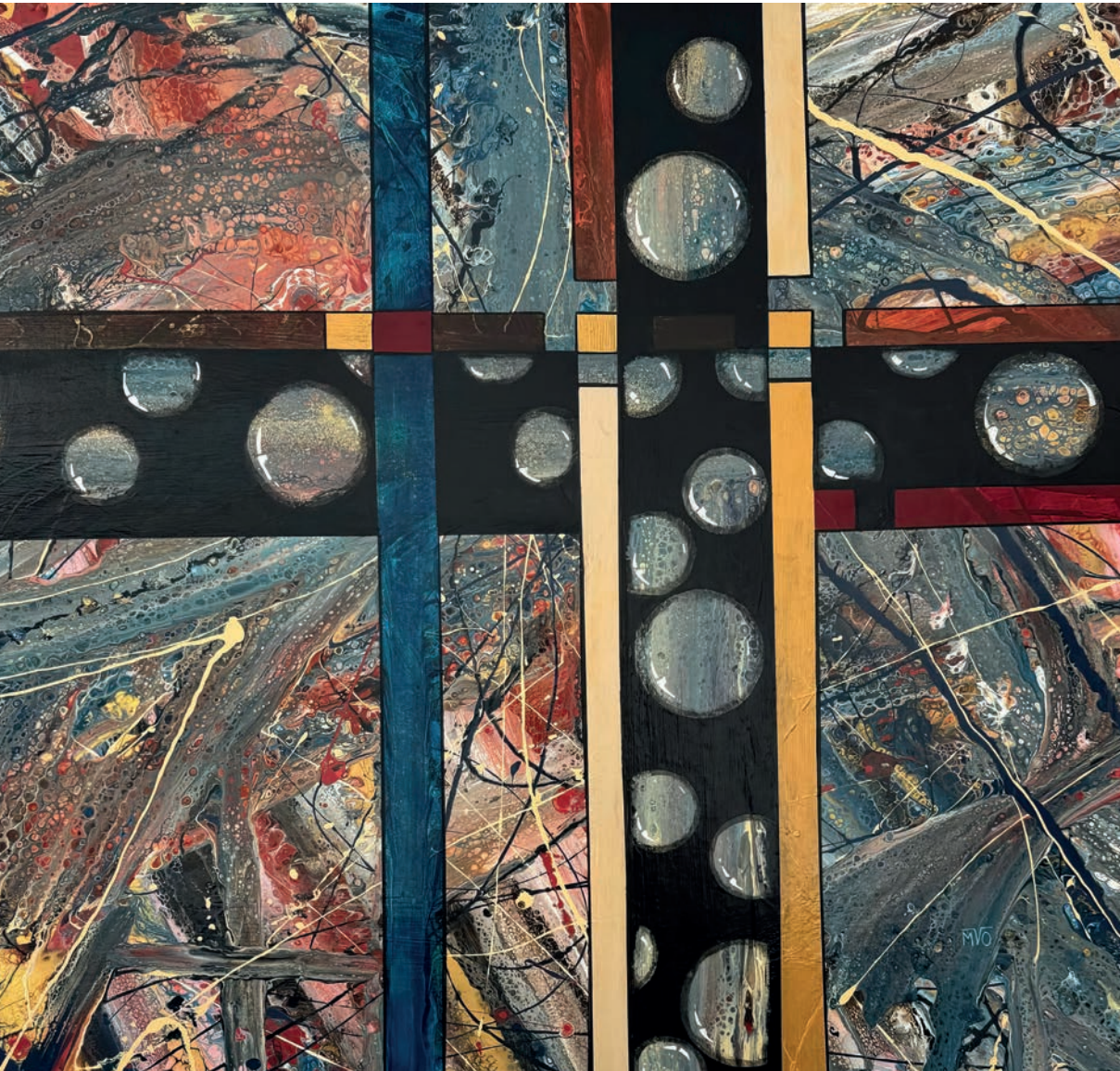
simultaneously, to create boundaries that distinguished them from UMCs. Identity work was performed to ensure that their history and domain focuses were coherent with the dominant mindset of their organization, while competence work was done to enhance their research infrastructure. The human dimension of the infrastructure received considerable attention: more research staff, time made available for doctors, and recognition that boundary spanners facilitate research collaborations.

Power work to find and mobilize strategic academic partners was mostly focused on complementary fields, as non-academic hospitals work in domains adjacent to those of academia. The TopCare hospitals tended to avoid power conflicts, resulting in a preservation of the status quo favoring academia.

The local research history, strategic domain focus, in-house expertise, patient flows, infrastructure, and network relationships of each TopCare hospital influenced collaboration with academia (cf. Currie et al, 2013; Waring et al., 2020). Increased coherence between the different forms of boundary work led to productive research collaborations and generated research impact. To meet future requirements, such as regionalization, further boundary work is needed to create long-term collaborations and new ways of rewarding research collaboration within organizations.

Chapter 6

Discussion and Conclusion



Introduction

This thesis focuses on governance practices in medical research and aims to explore how various actors within different regulatory frameworks interpret and operationalize ethical and scientific values, translating them into actions to safeguard these values in practice. I have examined the institutional work done by these actors to align these key values with research practices. This approach sheds light on much of the often unnoticed and unrecognized work that is undertaken to ensure and enhance research quality and to reinforce ethical and scientific values within research. When a value requires emphasis, affirmation or relevance and one or more actors are held responsible, disparities emerge regarding which values take precedence over others, how they relate to one another, how they can be implemented in practice, and whether they are properly safeguarded. Ultimately, this thesis provides insights into areas where the governance of medical research in the Netherlands can be improved. It searches for an answer to the main research question: What forms of institutional work are undertaken by public and private actors to address dynamic challenges within the multilevel governance structure of medical research in order to ensure the protection of research participants and scientific integrity, and to attain research impact?

To increase our understanding of the work actors need to do to respond to dynamic challenges to ethical and scientific values within and between different levels of governance in medical research, I studied four different levels of governance practices in medical research. These governance practices are related to the four sub-questions that complement the main research question:

1. How do different actors respond to changes originating from European Union (EU) regulation within layered legislative systems? (Chapter 2)
2. How do public supervisors of ongoing clinical trials in the Netherlands respond to the external challenges in the Dutch regulatory regime? (Chapter 3)

3. How are systems that ensure he data quality in investigator-initiated trials organized in Dutch hospitals? (Chapter 4)
4. What is the impact of research collaboration on medical research output in Dutch hospitals and how do TopCare hospitals initiate and improve productive research collaborations? (Chapter 5)

In the next section I highlight and discuss the key findings for each sub-question, culminating in a synthesis of the results, and answer the main research question in the final sub-section. I then reflect on the theory and methodology used, give recommendations for further research, and reflect again on the illustrative case presented in the introduction. Finally, I formulate recommendations for the governance of medical research.

Main findings

This thesis examined the intricate interplay between actors, practices and institutions governing medical research. It elucidated the institutional work undertaken by actors to achieve and create workable solutions and practices. At the heart of this institutional work lie ethical and scientific values that form the foundation for these interactions. These key values serve as an institutional moral compass, shaping both written and unwritten rules for professions and organizations (Van Es, 2015). Ethical and scientific values constitute the primary focus of the Medical Research Involving Human Subjects Act (WMO). On the one hand, the act aims to protect research participants from the risks and burdens of scientific research (e.g. through ethical approval by an accredited Medical Research Ethics Committee or MREC); on the other hand, it does not wish to unnecessarily hinder the progress of medical science (Stukart et al., 2012, Timmers et al., 2023). As always when both scientific and ethical goals are involved, it is an ongoing challenge in practice to integrate them holistically. In other words, the governance of medical research has as its aim the establishment of responsible research practices (Pimple, 2000; Ajuwon, 2020).

As outlined in section 1.1, adopting a governance perspective allowed me to identify three governance mechanisms: rules, room and responsibilities, represented within a triangular framework. These mechanisms ensure the

protection of ethical and scientific values through a series of interactions. The significance of key ethical and scientific values is not up for debate, but in their enactment they need to be translated to specific situations. Moreover, the process of safeguarding them in practice takes place in a dynamic institutional environment, the result of EU legislation, technological and methodological advancements, legislative evaluations or incidents and their impact on the diverse (and partially overlapping) responsibilities of various actors engaged in the review and supervision of medical research (Chapters 2-4).

This thesis provides insights into the interwoven nature of the three governance mechanisms and their potential to either reinforce or hinder one another, with a certain synergy being required to ensure and enhance the quality and output of medical research while safeguarding key values. In analysing this dynamic, I focused specifically on the institutional work employed by actors in the governance of medical research. Further discussions of each governance level expound upon these insights, demonstrating the potential interplay between distinct governance mechanisms and showing that interdependencies between actors play a role in how effectively these mechanisms can be implemented.

The first two empirical chapters of this thesis adopt a regulatory perspective, encompassing a broad range of regulations and standards of good clinical practice that serve as a guiding force in the governance of public supervision.

How do different actors respond to changes originating from EU regulation within layered legislative systems?

The study covered in Chapter 2 investigated the effects of implementing the EU Clinical Trial Directive (CTD), an attempt to harmonize the supervision of clinical trials across the European Union. Its purpose was to improve the protection of research participants in clinical trials by setting up a centralized supervision system. The system entailed establishing one competent authority in each Member State and requiring approval for clinical trials to be obtained from both this competent authority and a separate ethical committee. Implementation became particularly challenging in the Netherlands due to the disparities between the CTD and the Dutch framework

of public supervision. Before the European Union developed a regulatory regime for clinical trials, the Netherlands had already developed a decentralized structure, including MRECs that conduct integrated evaluations of ethical and medical-scientific values. This approach diverged from the model outlined later in the CTD. While the Netherlands has a complex decentralized institutional structure involving multiple competent authorities – the CCMO, the Health and Youth Care Inspectorate (IGJ), and the Medicines Evaluation Board (CBG) – the CTD is based on a single competent authority.

Chapter 2 showed the impact of implementing the CTD in the Netherlands and how this has led to specific forms of institutional change through the institutional work performed by actors in the system. The study analysed the discrepancy between policy objectives and actual implementation, highlighting the complexities and challenges of achieving harmonization across Member States. The study revealed how CTD implementation has led to new governance levels in the Netherlands, , resulting in a fragmented supervisory structure. The responsibilities designated to the competent authority outlined in the CTD have been divided among the key players in public supervision, i.e. the IGJ, the CCMO, the Ministry of Health, Welfare and Sport, and the CBG. This is because the assignment of tasks in the CTD did not correspond one-to-one with the situation in the Netherlands, which has a different review system than the EU had envisioned. As this system remained intact, the responsibilities had to be divided and allocated among the existing parties, which led to the WMO being amended without eroding the Dutch system. New institutions were introduced alongside existing ones (layering) and the organizational structure of public supervision in the Netherlands became (more) complex and fragmented. This in turn triggered institutional work by stakeholders, such as coordination and alignment work, but it also initiated incremental institutional changes.

The new division of responsibilities also led to overlapping roles in the supervision of ongoing trials, however, resulting in ambiguity (institutional drift) among such entities as the IGJ and MRECs. The IGJ supervises clinical trials and gathers information from trial sponsors but lacks the authority to halt research trials in the event of unacceptable risks. That power is held by MRECs, but despite this authority, they lack the resources needed for

thorough supervision because they are excluded from public funding. This mutual dependence between the IGJ and MRECs is mediated through the CCMO, which supervises the MRECs. Consequently, there is limited practical room for facilitating a direct relationship between the IGJ and the MRECs, making it difficult to fine-tune and adjust their shared responsibilities and posing a challenge to any active alignment with the CTD through institutional efforts.

The findings of this study revealed that despite efforts to centralize and coordinate the regulation of clinical trials through EU harmonization, the Netherlands experienced increased fragmentation within its regulatory framework and overlapping responsibilities, a deviation from the intended harmonization. This study showed the necessity of a cautious and meticulous implementation of harmonization policies to avoid unintended consequences that could undermine the directive's objective, which is to ensure both the protection of research participants and the enhancement of medical research.

How do public supervisors of ongoing clinical trials in the Netherlands respond to the external challenges in the Dutch regulatory regime?

The study described in Chapter 3 explores how, over the past two decades, regulatory bodies supervising ongoing clinical trials in the Netherlands responded to external challenges brought about by international factors, such as EU harmonization, and national factors, including critical incident reviews. The study investigated how various stakeholders engaged in the public supervision of ongoing clinical trials responded to the dynamic landscape of regulatory changes and addressed a range of challenges, including EU harmonization policies. The regulatory perspective of the EU emphasised the role of rules, with a broad range of regulations and standards of good clinical practice serving as a guiding force in the governance of public supervision.

The Propatria case, which occurred in a university hospital, concerned a study in which the treatment under investigation led to more deaths among patients than the placebo. It was a significant incident that had several effects. First, it led to responsibilities being clarified between the various supervisory bodies, with the Ministry of Health taking action and initially

dividing roles between the CCMO and the IGJ in response to recommendations arising from the initial WMO evaluation. Subsequently, it led to forced collaboration between the IGJ and the CCMO, with the initial focus being on averting conflicts and fostering room and flexibility to navigate their intricate relationship during coordination meetings. Collaboration between them promoted alignment and the establishment of practical agreements for ad hoc information-sharing. As time went on, they collaborated more closely, allowing them to better handle their responsibilities and better coordinate their supervisory tasks.

Second, the Propatria incident highlighted the critical nature of ongoing trial supervision by MRECs. The result was that the reporting of Serious Adverse Events (SAEs) to MRECs was made mandatory for all studies governed by the WMO, to ensure participant safety. Mandatory SAE reporting was integrated into daily practice following an amendment to the WMO in 2015 (assignment). However, because MRECs affiliated with University Medical Centres (UMCs) or non-academic teaching hospitals faced financial constraints, timely protocol review remained their primary focus; this came down to a strict interpretation of their assigned role under legislation, limiting their ability to adapt to external challenges.

Third, the Ministry of Health assigned a new responsibility to the CCMO: annual reporting on the number of SAEs and the consequences for the safety of participants. Before being required to take on this obligation, the CCMO had proactively created sufficient room and flexibility to explore practical solutions that would lead to enhanced review practices. It then developed a digital tool to facilitate SAE reporting.

Fourth, the incident highlighted the Boards of Directors' (BoD) role as sponsors of investigator-initiated trials (IITs) and their accompanying supervisory responsibilities under the WMO (assigning). As research activities at teaching hospitals expanded and they increasingly positioned themselves as research entities, the IGJ initiated inspections of these hospitals. Taking an exploratory and flexible approach, the IGJ piloted a new methodology by developing a database from which it selected teaching hospitals for inspection. The IGJ concluded its inspections earlier than anticipated, citing a

recurring issue in the teaching hospitals it had inspected: the need to establish and integrate a comprehensive quality system, encompassing auditing and monitoring processes. The IGJ encouraged and mandated teaching hospital BoDs to accept and fully embrace their responsibility as sponsors. A further factor was the involvement of an actor outside the established regulatory framework: the teaching hospitals association (STZ), which developed standard operating procedures to complement quality assurance manuals in these hospitals and facilitated the exchange of lessons learned and best practices.

Research questions 3 and 4 address the trend of Dutch teaching hospitals increasingly undertaking medical research activities. The next sub-section, which focuses on research question 3, examines the implementation of safety monitoring for IITs within teaching hospitals and UMCs. It explores how various stakeholders collaborated to translate the legal requirements for monitoring and data integrity into everyday practices, and examines the resulting effects on key research values.

How are systems that ensure the data quality in investigator-initiated trials organized in Dutch hospitals?

Chapter 4 of this study investigated the organizational structures of Quality Management Systems[24] (QMSs) for IITs within Dutch hospitals. The regulatory framework governing IITs posed significant challenges for hospitals, prompting them to explore alternative approaches so as to comply with new requirements or to safeguard values. Conventionally, monitoring served as the standard quality assurance method for ongoing trials, in line with good clinical practice and international guidelines. However, my research findings revealed that, in practice, the prevalent approach to implementing monitoring programmes more closely resembles mentoring. I found that both monitoring and mentoring incorporate elements of compliance and practical feedback for learning purposes. Within monitoring-oriented settings, the flow of learning primarily occurs unidirectionally from the monitor to the researcher, whereas mentoring-oriented settings foster mutual support and reciprocal learning.

[24] My research question in Chapter 4 focused primarily on data management. A QMS has a broader scope, however, including such components as training in GCP and developing guidelines and Standard Operating Procedures.

The roles of monitors and mentors revolve around interpreting regulations and raising awareness when supervising researchers on site. Full compliance may not always be feasible due to resource constraints and the nature of the learning environment. The learning approach varies between the two settings: in monitoring, the monitored party learns how to conform to rules and adheres to key values under the monitor's guidance. In mentoring, there is mutual learning and support, often with role-switching flexibility, and relevant rules and key values also play a crucial role. Both monitors and mentors play a facilitating role in promoting tailor-made, responsible research conduct, and both encourage researchers to ensure key ethical and scientific values.

How challenges are addressed within each system depends largely on the authority of the hospital's BoD and their relationships with staff members. Chapter 4 discussed the challenges faced by the BoD and staff in maintaining a holistic view of the diverse components of QMSs and in striking the right balance between accountability and learning. BoDs, acting as sponsors, increasingly embraced their responsibility for QMSs in IITs, as detailed in Chapter 3. The Propatria incident and subsequent inspection visits emphasized the need for improved monitoring to ensure participant safety and data integrity during trials. These developments, along with facilitatory support from the STZ, have opened avenues for experimenting with new mentoring practices, particularly in teaching hospitals. Interestingly, all these mentoring practices have adopted the NFU risk classification.

The UMCs and teaching hospitals offered mentors, monitors, and researchers a setting and environment conducive to learning. This included providing practical support to GCP-qualified researchers in aligning their research procedures to the legal requirements. Consequently, both monitoring and mentoring became integral components of Quality Management Systems within teaching hospitals and UMCs. The BoD had delegated responsibility for implementing these systems to staff departments, which became responsible and accountable for quality control, improvement and assurance of IITs, while the BoD, as sponsors, retained overall responsibility.

In research question 4, I investigated the strategic steps taken by selected non-academic teaching hospitals that had been granted sufficient resources to position themselves as attractive and credible research partners.

What is the impact of research collaboration on medical research output in Dutch hospitals and how do TopCare hospitals initiate and improve productive research collaboration?

To assess the impact of research collaboration in all Dutch hospitals on medical research output, and to understand how hospitals initiate and enhance productive research collaborations, I adopted a mixed-method research design focusing on the key scientific value. This value emphasized generating reliable, accurate results with societal benefits, measured through research impact proxies. I therefore measured the number and type (single-institute, national, international) of collaborative publications in all eight UMCs and 28 non-academic teaching hospitals.

This bibliometric analysis revealed an upward trend in international collaborations across all hospitals, paralleled by a downward trend in national collaborations and single-institute research. Notably, collaborative efforts, especially international ones, resulted in higher impact scores compared to national collaborations. Non-academic teaching hospitals often published in conjunction with UMCs, whereas the scenario was notably different for UMCs, which had significantly fewer collaborative publications with non-academic hospitals. This discrepancy suggested that collaboration between non-academic teaching hospitals and UMCs might be more prevalent among non-academic teaching hospitals and have a higher impact for them than for UMCs.

Second, this study investigated the research collaboration dynamics of two non-academic teaching hospitals participating in the TopCare programme, which receives Ministry of Health (ZonMw) funding for medical research and highly specialized care. The results of the bibliometric analysis highlighted their leading position within their specific domains. Ethnographic analyses furthermore uncovered several boundary work mechanisms utilized by non-academic TopCare hospitals to foster research collaboration. These mechanisms included aligning research activities with organizational

mindsets, investing in research infrastructure, and establishing strategic academic partnerships. Ethnographic interviews with TopCare programme stakeholders shed light on institutional boundary work undertaken by these hospitals. This work, guided by the concepts of identity work, competence work and power work, as outlined by Santos and Eisenhardt (2005), focused on fostering and improving research collaborations with academia.

The selected non-academic teaching hospitals utilized the TopCare programme resources strategically. A requirement for funding was alignment with academia. The two non-academic hospitals therefore used the funding to refine their value proposition (identity) and to invest in materials and human resources that would enhance and digitize the research infrastructure (competence). Moreover, they aligned themselves with academia by choosing research partners that complemented their own strengths, leveraging their research history, domain expertise and patient flows (power). Boundary spanners, leading scientists in specific domains, played a pivotal role in bridging organizational boundaries and facilitating knowledge exchange.

In conclusion, the boundary work mechanisms adopted by non-academic TopCare hospitals reveal a dual dynamic in opening and safeguarding boundaries. On the one hand, they cemented their collaborative position and improved or reinforced scientific value in research collaborations with academia. On the other hand, they did not accomplish the underlying objective of the short-term TopCare programme, i.e. to establish structural funding for highly specialized care and medical research in non-academic teaching hospitals. The BoDs of both hospitals studied utilized their power to shape ZonMw's subsequent action: the follow-up funding programme to TopCare.

Main research question

In this section I answer the main research question: What forms of institutional work are undertaken by public and private actors to address dynamic challenges within the multilevel governance structure of medical research in order to ensure the protection of research participants and scientific integrity, and to attain research impact?

The landscape of medical research is continually being shaped by a myriad of dynamic developments, both external and internal. These include the introduction of EU directives and regulations, unforeseen incidents, changes in the research landscape, and periodic reviews of national legislation. Such changes reverberate across all levels of governance within the medical research community. One of the most notable consequences of these developments is the perpetual tension among the various actors, practices, and institutions involved. As new regulations and directives are introduced or other dynamic challenges arise, the actors feel a pressing need for recalibration and repair work. New rules will inevitably be added, and the question then is which ones and whether the system as a whole needs to be adjusted. In this process, actors constantly seek pragmatic solutions to activate, articulate and ensure key ethical and scientific values.

In the realm of governance within medical research, it is imperative for the relevant actors to collaborate effectively. This has been especially true in the Dutch context, where multiple actors are also engaged in review and supervision. Furthermore, the governance system of medical research has been subject to a complex and fragmented regulatory framework resulting from historical developments, such as the numerous local MRECs operating in the periphery. Such fragmentation has led to dependencies on the resources and actions of and interactions with other levels, affecting the accomplishment of system goals and tasks (Rhodes, 1996; Koppenjan & Klijn, 2004). Consequently, close coordination and collaboration among actors across all levels has become necessary (Peters, 1998; Pierre & Peters, 2000; Van Popering-Verkerk & Van Buuren, 2016). Examples of such coordination and collaboration as forms of institutional work include:

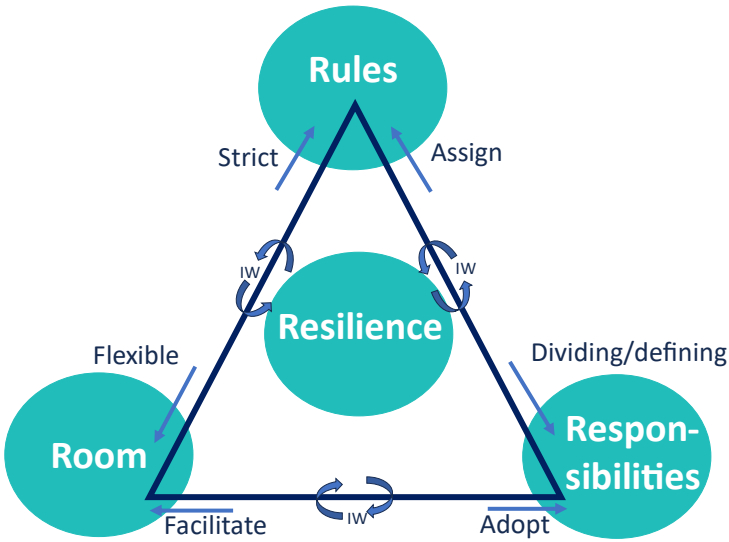
- at the supranational level: coordination by a competent authority (CCMO) to improve information flows, such as SAEs, in accordance with the CTD (Chapters 2 and 3).
- at the national level: collaboration between the CCMO and the IGJ, resulting in an agreement on the mutual exchange of information and coordination (Chapter 3); collaboration among UMCs and teaching hospitals in medical research, leading to joint publications with higher research impact scores (Chapter 5); and collaboration

between hospitals and their associations (NFU or STZ) to address issues identified through IGJ inspections and to exchange best practices (Chapter 3).

- at the local level: coordination work by staff members and collaboration with BoD to assure the quality of data management (Chapter 4).

Institutional work is an essential component of various governance practices for addressing dynamic developments effectively. Drawing upon these insights, I have devised a theoretical framework to illustrate the impact of these challenges. Through my observations, I have identified that actors' institutional work revolves around three interconnected governance mechanisms: rules, room and responsibilities, aimed at safeguarding ethical and scientific values (see Figure 6.1).

Figure 6.1 The conceptual 4R model



IW: institutional work

The conceptual 4R model, as depicted in Figure 6.1, is intended to be a dynamic model in practice.

‘Rules’ encompasses laws, directives, regulations, guidelines and standards that must be adhered to. ‘Room’ refers to the flexibility and autonomy that actors need to interpret and safeguard key values in specific practices within those rules. This flexibility matches with actors’ drive for change, learning and experimenting (Duit & Galaz, 2008). ‘Responsibilities’ entails allocating tasks and duties among different actors, which can lead to a high degree of interdependency in task execution in medical research. By collaborating effectively, actors can establish a resilient governance framework capable of addressing challenges and safeguarding the scientific integrity and ethics of medical research.

‘Resilience’ is defined as the capacity to prepare for, respond to, or recover from unforeseen problems or disturbances (Chandler & Coafee, 2016) and, as Meurs (2014) adds: ‘while maintaining key values’ (p. 9). In the pursuit of resilience, actors in the supervision and review system engage in institutional work to promote – whenever feasible – effective collaboration among actors, thereby fostering an optimal balance between rules, room and responsibilities. This necessitates providing actors with both structure and flexibility to respond to dynamic challenges. Achieving this balance optimizes the actualization of key values. Conversely, an imbalance between rules, room and responsibilities may compromise or impede the safeguarding of these values. In short, the aim of institutional work addressing the governance mechanisms of rules, roles and responsibilities is to attain a certain degree of resilience.

The conceptual 4R model aligns with findings by Meurs (2014). In her essay *From regulatory pressure to appropriate rules*, she discusses ‘a collective search for a dynamic relationship between freedom and rules. Rules are neutral in principle; they are at most a tool for organizing interactions, ensuring a certain level of predictability, and preventing unwanted arbitrariness’ (p. 9). This interpretation of the term ‘rule’ corresponds with the 4R model. Meurs, drawing from Berlin's work on freedom, recognizes two views of rules: rules can provide space (positive) or restrict (negative). Restriction is reflected in the 4R model under ‘strict and assign’. Providing space is classified under ‘room’ and encompasses two views: ‘facilitate’ and ‘flexible’. Meurs perceives responsibility as a virtue: ‘the ability to act as a

responsible individual, to bear responsibility without first asking whether it belongs to your task, competence, or domain' (p. 10). This matches the interpretation of 'responsibility' in the 4R model, which includes the view of 'adopt(ion)'.

Finally, Meurs (2014) states: 'Learning, improvising, and adapting while maintaining key values form the basis of resilient governance' (p. 9). According to Meurs, this requires trial and error, checks and balances, experiments, and allowing for variety. This interpretation of resilience, for example, aligns with Chapter 4 on mentoring and monitoring. Both variants aim to strike a balance among the three governance mechanisms and to maintain resilience in the face of new challenges and requirements, albeit employing distinct approaches to achieving this balance. Monitoring, as part of the scientific value (see §1.1), can be considered rule-guided; it entails adherence to strict rules, with compliance supervised by a professional monitor who fosters a meaningful research environment. In mentoring, these rules are more embedded in a horizontal relational process (peers), with compliance assessment conducted through 'another set of eyes', fostering mutual learning and reflection. In this context, monitoring remains an important scientific value but actors seek ways to reshape it in practice. Both variants adhere to the same regulatory framework but are embedded in different relational paradigms. However, mentoring appears to be more appropriate for IITs, which typically operate in environments with limited resources. In these settings, the learning process between mentor and mentee is more assured due to their non-hierarchical and equal relationship, mutual support, and the potential to reach a larger population of researchers.

Other findings support the need for various mechanisms in the governance of medical research (see Figure 6.1):

- The Ministry of Health has *assigned* a task to a legal entity (CCMO in case of SAEs) and *divided* duties among actors (IGJ and CCMO).
- The STZ has *facilitated* (has left room for) discussions among non-academic teaching hospitals, particularly as hospitals that had undergone IGJ inspections wished to share their findings; in this case the STZ *adopted* their role of facilitator.

- The IGJ has adopted a *flexible* stance toward hospital BoD, allowing them room to adjust to their legal responsibilities, with the IGJ expressing confidence in the *facilitating* role played by the STZ.
- The MRECs, affiliated with UMCs or non-academic teaching hospitals, have primarily focused on timely protocol review, adhering *strictly* to their assigned role in legislation.

The 4R model can be instrumental in diagnosing whether various governance mechanisms are balanced among interdependent actors. This study highlights that the division of tasks between the IGJ and MRECs in the supervision of ongoing trials is a contentious issue. The distribution of responsibilities is insufficiently clear in the existing regulations. Additionally, there is no scope to develop a direct relationship between the IGJ and MRECs since the CCMO acts as the latter's supervisory authority. Consequently, resilience cannot be demonstrated. The 4R model can also be used to indicate how this balance can be achieved. As one of the co-authors of the fourth evaluation report on the WMO, I find the current situation to be undesirable and have made recommendations for restoring resilience in the interdependent relationships. One recommendation is that the IGJ assume supervisory responsibilities for the MRECs, to be codified in regulations. This would eliminate the supervisory role of the CCMO over the MRECs, allowing room to strengthen the CCMO's coordinating role, to better align the CCMO and MRECs as review committees, and to create opportunities to rebuild the trust relationship between MRECs and the CCMO.

In the past 25 years, the WMO has been amended in response to the various crises that have arisen in clinical and medical research, as well to as the results of evaluations. It has thus evolved over time to accommodate changing circumstances and values (cf. Sandalow, 1981). To understand the changing meaning of values in practice, this study emphasizes the importance of observing the institutional work of actors addressing dynamic developments across three intertwined governance mechanisms: rules, room and responsibilities. As regulations undergo regular changes, this can lead to new or modified forms of interaction and interdependencies between actors and practices within the realm of medical research (Horstman & De Vries, 1989). Such continuous adjustments have diverse impacts on the three governance

mechanisms, illustrating their interconnectedness and potential to either reinforce or impede one another and also influence the extent to which resilience can be achieved.

Presently, the WMO's authority has diminished by the enactment of the European Union's Clinical Trials Regulation (CTR), Medical Devices Regulation (MDR), and In Vitro Diagnostics Regulation (IVDR). Certain provisions of the WMO have been declared inapplicable, with direct reference to EU legislation now being incorporated into the WMO. The WMO continues the supervising tasks and requirements of the CCMO and the MRECs, as well as their supervision and enforcement powers (Timmers et al., 2023). In light of these specific circumstances, the safeguarding of ethical and scientific values will likely evolve. The 4R model can be employed to monitor this process, a point I elaborate on below.

The final aspect of the research question concerns research impact. After conducting research, it is customary to publish the positive and negative findings. In research collaborations, this requires boundary crossing. To increase research impact at the national level, UMCs and non-academic teaching hospitals must collaborate on research and on publishing the related articles (Chapter 5). These collaborations appear to be more prevalent among and impactful for non-academic hospitals. Two non-academic teaching hospitals participating in the TopCare programme received additional funding that enabled them to invest in different types of boundary work, such as identity, competence and power work (Santos & Eisenhardt, 2005), to facilitate and establish research collaborations with academic partners, a funding requirement for this programme.

Reflection on research theory and methodology

Theory

This PhD research underscored the importance of examining institutional relationships and governance within a broader temporal framework. As highlighted by such scholars as Scott (2008), Mahoney and Thelen (2010), and Abdelnour et al. (2017), institutional fields seldom remain static; they often contain inherent differences, tendencies and contradictions that could

indicate forthcoming institutional change. In my research, I aimed to examine institutional changes in the governance of medical research practices by analysing dynamic challenges, such as EU harmonization attempts and incidents. By placing the dynamics that I studied within a historical context, I was able to discern how relationships evolved over time and what factors bring about change. In regulated environments such as the supervision and review systems in medical research, where actors are interdependent, adopting an institutional lens allowed me to understand the institutional work involved in fostering collaboration, coordination, and alignment among various stakeholders, all necessary to cope with challenges.

By collaborating with experts in this field, I gained insights into various institutional theories, including those of institutional change (Mahoney & Thelen, 2010) and institutional work (Lawrence & Suddaby, 2006), and analysed the research data acquired in cooperation with them. These institutional theories were intentionally broadly applied. Unlike Mahoney and Thelen (2010), I did not explicitly link each mode of institutional change with a specific type of agent. While terms such as coordination, alignment work or collaboration were occasionally used in the various chapters in this thesis, I did not associate all observed working activities with specific terms. My emphasis was primarily on illustrating the extensive work undertaken by actors within diverse governance practices to promote and safeguard ethical and scientific values. Additionally, I demonstrated the involvement of numerous actors within the supervision and review system of medical research, highlighting their varying degrees of interdependence and how the necessary coordination and collaboration between them unfolded. I also noted the emergence of new actors outside the legislative framework such as hospital boards and the STZ.

Despite the broad application of theories concerning the term ‘work’ in the chapters, it was noticeable that much of the work performed by the multiple actors to promote and safeguard ethical and scientific values falls under the concepts of institutional work and boundary work, often characterized as 'positioning work'. In the TopCare programme, identity work and competence work could be interpreted as forms of positioning work, as their aim was to strengthen the position of a hospital’s domain. Much of the institutional work

that actors conducted within review and supervision practices could also be described as positioning work, especially when actors were assigned new responsibilities or adopted responsibilities themselves, and enacted them within the available room and rules. This positioning work might have been essential for ensuring that these responsibilities corresponded with their own organizational identity and possibilities, and matched the responsibilities of other external collaborative partners. In other words, theories of institutional work and boundary work are instrumental in analysing how actors adhere to established rules. Meanwhile, the 4R model can assist in analysing and designing an optimal combination of rules, roles, and responsibilities for settings with interdependent actors, ensuring practical functionality.

Reflecting on past practices, I acknowledge instances where I may have approached the application of a theory too one-dimensionally. In Chapter 2, I delved into 'layering'. This phenomenon arose when, under the CTD, institutions were integrated into the WMO because the Netherlands was reluctant to relinquish its existing institutional arrangements. Layering was not only about regulatory institutions alongside old ones, however; it also involved delegating responsibilities originally assigned to a single actor (the competent authority) to multiple actors, as was the case when implementing the CTD. Various EU regulations have now come into force, one example being the CTR, which has suspended certain sections of the WMO and led to the emergence of multiple layers of regulation. A common argument furthermore suggests that EU regulations differ fundamentally from EU directives because regulations do not require transposition into national laws. My research shows, however, that substantial institutional work is still necessary within Member States, similar to the implementation of a directive, to ensure the effective functioning of EU regulations. For example, it has yet to be determined which actor will assume the role of supervisory authority and which enforcement mechanisms will be allocated to this actor. In both instances, then, layering is likely to occur to make existing regulatory frameworks fit into the changing international regulatory landscape.

One of the strengths of the selected theoretical lens lies in its examination of both endogenous, gradual institutional change and external sources of institutional change. Over time, these two approaches were found to be

interconnected. Chapter 2 of this study outlines various forms of gradual institutional change, such as drift and conversion. These findings subsequently served as precursors to institutional changes in later stages, which were deemed necessary to address or improve the situations identified. However, it was important to recognize that gradual institutional change may sometimes lead to unintended consequences, prompting the need for more fundamental reforms. For example, institutional changes within the IGJ and MRECs in the supervision of ongoing clinical trials resulted in drift due to the redistribution of responsibilities, leading to overlapping roles. Despite efforts to instigate change, this situation persisted, necessitating significant institutional reforms later on. The fourth legislative evaluation of the WMO proposed abolishing the CCMO's supervisory role in the MRECs' activities and transferring this authority to the IGJ (Timmers et al., 2023). This change is pivotal due to the CCMO's lack of formal enforcement mechanisms, and it may enhance the future resilience of the Dutch supervision and review system in the face of external challenges, such as new EU regulations. Additionally, a pattern of conversion was observed between the IGJ and pharmaceutical companies or CROs. Previously, the IGJ had limited authority over entities operating in an international context. However, new EU regulations enacted in 2021 (MDR) and 2022 (CTR and IVDR) have expanded its supervisory and enforcement powers, facilitating more effective supervision of studies conducted in the Netherlands on behalf of multinational companies. These changes necessitate a reassessment of the relationship between the CCMO and the IGJ.

It is noteworthy that actors in medical research often refrain from explicitly discussing ethical and scientific values but instead tend to employ the technical terms of the regulation in discussions. This phenomenon, ‘moral muteness’, may arise due to factors such as delegation of responsibility, fear of disrupting harmony, concerns about efficiency, and power dynamics (Bird & Waters, 2005). Discouraging an open discussion of values can contribute to a culture of silence (Verhezen, 2010). Conversely, countering moral muteness involves emphasizing moral arguments, engaging in moral conversations (Brinkmann et al., 2016), including a dialogue about moral assumptions and perspectives among actors (Kremer & Ottes, 2023), and undertaking morally principled action (Csillag, 2019). It is therefore crucial that these implicit

references to key values be made explicit. For instance, rather than assuming that compliance with regulations indicates adherence to ethical and scientific principles, researchers in monitoring or mentoring practices should openly discuss and articulate the specific ethical and scientific values guiding their decisions and actions. In monitoring practices, the monitor may be required to adopt a leadership role in instigating such discussions, while in mentoring practices, staff can facilitate this discourse by adopting an approach centred on mutual learning and reflection. Overall, actively addressing and safeguarding ethical and scientific values serves as an essential tool for fostering ethical awareness among the actors involved.

This research demonstrates the ongoing need for reflection on the ethical and scientific values in the medical research sector, despite the existing high level of awareness regarding the importance of these values. This perpetual reflection is essential due to the potential for values to conflict and the inherent need for pragmatism in ensuring their application. Perfect guarantees are impossible in actual practice, as discussed in the chapters on the public supervision of clinical trials (Chapter 3) or monitoring (Chapter 4). Moreover, this study emphasizes the crucial role of visibly safeguarding ethical and scientific values in the day-to-day activities of researchers, in addition to the discussions held in MRECs concerning individual protocols. Increasing the visibility of these values can enhance ethical awareness within the research community and its responsibility to actively promote and safeguard these key values in medical research. Furthermore, it can incentivize actors to take responsibility for their actions and decisions in research, both internally within their own organization and externally towards supervisory bodies and the public. Collectively, these efforts can help cultivate trust in the value and necessity of conducting medical research.

Chapter 5 highlights collaboration between UMCs and non-academic hospitals and illustrates the importance of both national and international collaboration in medical research in achieving research impact. Employing the framework proposed by Santos and Eisenhardt (2005) has proven beneficial in elucidating the boundary work that non-academic hospitals undertake to become attractive collaboration partners. Chapters 4 and 5 both underscore, in their respective ways, the importance of research integrity in practice,

emphasizing the organizational duty of care to foster a working environment where sound research practices thrive (KNAW et al., 2018). Chapter 4 accentuates the critical role of designing and implementing QMSs for IITs, encompassing training in GCP, monitoring and/or mentoring. Chapter 5 highlights the significance of competence work, entailing investment in and enhancement of research infrastructure within the domains of non-academic TopCare hospitals. Additionally, it emphasizes the importance of facilitating meetings within or across domains in a TopCare hospital, as well as among TopCare hospitals, and participating actively in research networks to promote knowledge-sharing and learning.

Methodology

Overall, the findings obtained from the qualitative and quantitative methods presented in this thesis are subject to certain limitations. First, they were influenced by my individual perceptions of what is important and relevant. The information and insights shared by the respondents have influenced my subsequent steps and choices for the research design and methodologies. For example, the WMO research project in 2014 (Grit & Van Oijen, 2015) sparked my interest in monitoring practices for IITs in hospitals. Second, the data collection period was constrained, and significant changes occurred in the external environment afterwards, including the enactment of various EU regulations. While I devote attention to these regulations in the articles that I co-authored, I was unable to address their actual impact on practice in this thesis due to the delayed implementation of the EUCTR. Through my involvement as a researcher in the fourth legislative evaluation of the WMO in 2023, I gained insight into the impact of EU regulations on practice through interviews and focus groups. It became apparent to me that institutional work by actors such as MRECs remained essential to maintaining the functionality of the review system.

In essence, adopting a contextual and longitudinal perspective was crucial for studying governance effectively. In some of the studies covered here, the researchers involved interviewed the same respondents multiple times, and these follow-up conversations helped them to continue building upon the results and interpretations that they had elaborated. I furthermore shared the interim and final results (papers) with the respondents wherever possible,

in addition to member checking. Future instances could enquire more explicitly as to how the study has influenced respondents' views on the research theme and/or actions. In subsequent research, I would also employ a participatory research design to utilize the knowledge of respondents /participants throughout the research lifecycle (Olmos-Vega et al., 2023).

Taking the methods used in my research a step further, I believe that analysing diverse practices and sharing experiences across different contexts can also give rise to valuable lessons in organizations in other countries that face similar challenges in the governance of medical research and the preservation of ethical and scientific values.

The primary aim of my research was to explore and elucidate patterns in and insights into the institutional work of actors addressing ethical and scientific values in order to deepen our understanding of these phenomena. Ethical and scientific values are not easy to measure, however, as they are embedded in laws and regulations and actualized by actors in practices and collaborative relationships. I found that, particularly in collaborative relationships, the quest for an appropriate allocation of responsibilities is important when there are interdependencies among actors. By examining their work, I have gained an impression of how they deal with these key values, how these values are prioritized in practice, and whether they conflict. I found that this depends on the context and the way actors interact with one another. Additionally, there is a need for creativity and experimentation (room) to continuously balance the various values against one another in an environment where collective learning and improvement are possible (Kwaliteitsraad, 2019).

Recommendations for research

Lessons learned from this research can provide valuable insights for future studies on values and governance in medical research. Ensuring the continued protection of ethical and scientific values in research practices requires a multidisciplinary research approach that integrates the expertise of MRECs as specified in the WMO (Article 16 paragraph 2a) – i.e. medical, legal, ethical, methodology and research participants' perspectives – supplemented by sociological, public administration, and governance perspectives (see

Recommendations for the governance of medical research). Policymakers, researchers, ethicists, medical professionals, administrators, lawyers, legal experts, social scientists and healthcare stakeholders can all benefit from multidisciplinary research. The added value of a governance approach lies in making the interpretations and work visible that are necessary to uphold ethical and scientific values in practice. By gaining a deeper understanding of governance in medical research, stakeholders can enhance their governance and other practices, policymaking, regulatory frameworks, and ethical considerations. This can lead to better protection of the rights and interests of research participants, improved quality of research, and a more balanced approach to innovation and public safety in medical science. In short, it is essential that stakeholders in medical research ensure expertise in governance within their own organizations; this is particularly true for the (future) coordinating role of the CCMO. Future research could therefore focus on exploring stakeholders' interpretations of values when addressing governance challenges in medical research. Building on Song's (2014) suggestion that understanding stakeholders' values can enhance governance outcomes, researchers could delve deeper into how these values align with governance frameworks. Qualitative enquiries, such as interviews or focus groups, could serve to uncover the nuances of stakeholders' value systems and their implications for governance in medical research. Comparative studies across different contexts or countries could provide insights into the variability of stakeholders' interpretations and their impact on governance practices. Ultimately, such research could help design governance mechanisms that better reflect stakeholders' diverse needs and perspectives, promoting ethical conduct and accountability in medical research.

Future research in medical science, especially research addressing the integration of artificial intelligence (AI) and other emerging technologies, offers a promising avenue for exploration. With the rapid advancement of AI, machine learning and big data analytics (Timmers et al., 2023) comes a growing need to investigate their implications for various aspects of medical research, including governance and ethical considerations. Throughout my doctoral journey, I have observed first-hand the impact of technological

advances. For example, for a previous article on clinical research publications (Van Oijen et al., 2005), I constructed a database manually, whereas now I obtained the publication data used in Chapter 5 through the CWTS database (Van Oijen et al., 2024).

Overall, future research into values and governance in medical research should continue to adopt a holistic and interdisciplinary approach that considers the historical context and interactions among different governance levels. By doing so, we can advance our understanding of how governance systems effectively promote ethical research practices while fostering innovation and scientific progress. Ensuring that the design and conduct of all research are ethically and scientifically sound is the responsibility of all those involved, including researchers, sponsors, MRECs, regulatory bodies and research participants (cf. Slowther et al., 2006).

Reflection on the illustrative case study

I started this thesis with an illustrative case. We will now return to it. Although the ethical and scientific values involved in conducting medical research with human participants are universally acknowledged, their manifestation in practice is observed in the institutional work of actors, which is often mediated and enacted through the governance mechanisms of rules, room and responsibilities. The illustrative case shows how the science coordinator adopted and assigned responsibilities to ensure processes were workable and streamlined.

In accordance with the rules stipulated in the WMO, it was mandatory for every research project to undergo prior review by an MREC, which would assess the ethical and scientific integrity of each research protocol. Without a favourable decision from this committee, the project could not proceed. Subsequently, the science coordinator assumed responsibility for establishing a registration system for research protocols that had been approved by an MREC. By fostering a trusting relationship with the various MRECs and studying the approved research protocols, she created the necessary room to facilitate and implement the registration system effectively. By utilizing governance mechanisms, including rules, room and responsibilities, she

achieved resilience, ensuring transparency regarding the studies that had been approved. This system allowed the science coordinator to contact the researchers and explain the support provided by the hospital, aimed at facilitating a learning environment for and supporting knowledge transfer among them (see Chapter 4: Lunch meetings and GCP training, and Chapter 5: Meetings within or across domains in a TopCare hospital). It served as a crucial initial step in ensuring the effectiveness of the quality system envisaged and in promoting and safeguarding key values.

The STZ stipulated rules mandating the implementation of a monitoring system, with the responsibility resting upon the sponsor. In the case of IIT, this responsibility was assigned to the BoD. The Board of Directors delegated the responsibility of designing and implementing a monitoring system to the science coordinator. To develop such a system, the science coordinator formulated a monitoring plan, which the BoD approved. This plan afforded her the flexibility and room to implement the monitoring system in stages, which involved such activities as recruiting and training monitors and developing monitoring formats. The science coordinator engaged in institutional work, in that she transposed the rules regarding monitoring into a practical and suitable approach for her own hospital that aligns with the guidelines set by the BoD. That approach had to be easily explainable, workable for researchers, and serve for accountability purposes with the Inspectorate. Moreover, the scientific coordinator needed to effectively address such challenges as mentor recruitment, which required the power and authority of the BoD. One feature of institutional work is that it requires significant deliberation, alignment, and coordination work. This goes beyond such routine tasks as conducting meetings or filling out forms. In the end, the point of all the work is to ensure that ongoing research is being monitored effectively, thereby safeguarding ethical and scientific integrity, enhancing performance and proactively mitigating potential problems (Love et al., 2022). As a consequence, the approach chosen in the illustrative case served as a crucial tool for fostering a research culture within the hospital that focused on bringing researchers together, as outlined in Chapter 4. It could, finally, be referred to as mentoring, as the work is conducted by peers.

Recommendations for the governance of medical research

In this thesis, I have examined how actors operate within various governance practices at both policy and organizational levels. By analysing these institutional environments, I observed how actors are constantly in motion and engage in institutional work to address external and internal dynamics while simultaneously promoting and safeguarding key values. Based on these findings, I developed a conceptual model, the 4R model, that emphasizes mutual alignment and coordination in performing institutional work and focuses on the three governance mechanisms of rules, room and responsibilities, the 3Rs. This framework visualizes how resilience is achieved in a specific governance practice, such as a review or supervision system. I observed how actors use the 3Rs to address challenges resulting from changes in the institutional environment and/or in the research landscape, creating workable practices and ensuring the safeguarding of key values. In my research, it became apparent that achieving a comprehensive understanding of governance in medical research entails simultaneously investigating the three governance mechanisms used to promote resilience and safeguard key values and discerning how they collectively influence governance processes and outcomes.

The intentions underlying various regulations, rooted in key values, could serve as a moral compass for actors in this field. My research shows that the actors were engaged in a continuous quest to determine what was needed to accurately identify any hindrances and to navigate around them. This quest consistently involved mediating between the intentions of the law and what this implied for their own actions in practice, as well as the necessity of adapting a law to the changing circumstances that influence these values. During the course of this research, the WMO has been amended several times. For example, the CCMO was assigned the additional responsibility of disclosing the SAEs received by MRECs year-by-year, using technology to do so. This responsibility was officially confirmed by an amendment after the CCMO was given some time to experiment and refine the method. This room proved to be an important institutional arrangement that allowed the CCMO to gradually build expertise in this field. In other cases, key values served as reference points for interdependent actors on how to interact with one

another and coordinate their work to meet their shared responsibilities regarding these values. Collaboration between the CCMO and IGJ needed to be fostered and established anew to promote and safeguard the key values. The Ministry of Health clarified their prescribed responsibilities, as outlined in rules, affording these stakeholders the opportunity and the institutional room to refine them in practice.

The EU presently plays and is expected to continue playing a substantial role in regulating medical research involving human participants, as part of its efforts to harmonize regulations. In light of these efforts, it is imperative to consider how best to future-proof the Dutch supervision and review system. The fourth evaluation of the WMO outlines several recommendations for comprehensive adjustments to the governance structure and demonstrates the pivotal role of institutional room. This is essential to ensure a balanced triangle of governance mechanisms. Adjustments to institutional room are often required in response to dynamic challenges. This entails fostering room for debate or for initiatives within a predefined framework, as specific rules apply and certain responsibilities are assigned. As co-author of this evaluation, I explain the importance of institutional room below, across four separate topics.

First, the fourth legislative evaluation of the WMO proposes solutions to the problem of the CCMO's dual responsibility for supervising MREC activities while also standardizing these activities through guidelines and supporting the MRECs. Various remedies are suggested, such as restructuring the responsibilities of the CCMO by discontinuing its supervisory function and transferring this responsibility to the IGJ. This would enhance the coordinating role of the CCMO and allow it the necessary institutional room to promote and organize collaboration within the review system (Timmers et al., 2023).

Second, the pharmaceutical industry often advocates EU regulation and harmonization, utilizing its resources and compliance capabilities as covert influences (Sismondo, 2018). The regulatory landscape of clinical trials, which takes its shape from the pharmaceutical industry, may not always be conducive to the needs and capabilities of researchers conducting IITs. Such

studies face significant challenges due to their limited resources and support compared to those available to pharmaceutical companies. The complexity faced by hospital-based researchers has further escalated with the introduction of EU regulations. Despite these challenges (strictness in rules and defined responsibilities), investigator-initiated studies often have significance for society, as they are driven by clinical imperatives rather than commercial interests. However, complex and detailed requirements, such as those of EU regulations, can also serve as impediments and influence the type of research being conducted. Important topics for legislative evaluation include formulating a vision regarding IITs by such entities as the STZ, the NFU and hospitals, identifying researchers' support requisites, and facilitating IITs within hospital settings (Timmers et al., 2024). In other words, institutional arrangements that create room to ensure the viability of IITs deserve full attention in the forthcoming evaluations.

Third, for several years now legislative evaluations have suggested that participant information has become increasingly comprehensive and detailed. This has resulted in a tension between the need for completeness and clarity, representing a conflict within the same ethical value. Sponsors such as pharmaceutical companies may find extensive participant information less burdensome due to its role in reducing liability, but this is not always the case for researchers conducting IITs. The obligation to safeguard participants entails more work and expense, potentially impeding the progress of research, particularly within an environment with restrictive budgets. The responsibility for this topic has been handed over to the Ministry of Health in the latest evaluation (Timmers et al., 2023). This implies that the Ministry should facilitate institutional room to enable both a debate among actors and diverse initiatives from actors in the field to improve participant information.

Fourth, the evaluation scarcely addresses monitoring issues. It expresses support for one request by a researcher that monitoring should take the applicable regulations into account (Timmers et al,. 2024). The problem, however, is that monitoring is typically provided too late, after the research has already commenced. The recommendation is for research to be categorised into a legally regulated risk classification system covering the risks

incurred by research participants through their involvement. This would offer research participants better protection and provide clarity and predictability for researchers regarding the requirements to be met (Timmers et al., 2024). Additionally, this thesis suggests that entities such as the IGJ should recognize initiatives such as mentoring as viable alternatives to monitoring. Not doing so would restrict the leeway needed to implement mentoring.

To conclude, responding effectively to evolving circumstances in medical research necessitates the integration of the governance mechanisms of rules, room and responsibilities. These mechanisms collectively ensure that actors within each governance practice learn, improvise and adapt while upholding key ethical and scientific values (cf. Meurs, 2014). Rules provide the normative framework for governing actions and offering clarity and consistency in decision-making. Room enables flexibility, innovation and adaption to dynamic conditions, while responsibilities delineate the obligations and accountabilities of stakeholders. By balancing these three mechanisms, governance practices can promote resilience by fostering coordination, collaboration and communication among stakeholders and by facilitating the continual evaluation and refinement of strategies (institutional work). Maintaining the integrity and reliability of scientific endeavours amidst dynamic challenges and opportunities requires balancing scientific goals with ethical values, such as minimizing risks to research participants and ensuring informed consent. The synergy of rules, room and responsibilities empowers actors to navigate the complexities inherent in medical research, safeguarding the resilience needed to promote ethical and scientific values.

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List of Abbreviations

AWT	'Academische Werkplaats Toezicht'
BoD	Board of Directors
CCMO	Central Committee on Research Involving Human Subjects
CTD	Clinical Trials Directive
CTR	Clinical Trials Regulation
CWTS	Center for Science and Technology Studies
EMA	European Medicines Agency
EU	European Union
GCP	Good Clinical Practice
IC	international collaboration
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ICH GCP	International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice
IGJ	Health and Youth Care Inspectorate
IIT	Investigator-initiated trial
IVDR	In Vitro Diagnostics Regulation
MDR	Medical Devices Regulation
MREC	Medical Research Ethics Committee
MNCS	Mean Normalized Citation Score
MNJS	Mean Normalized Journal Score
NC	national collaboration
NFU	Netherlands Federation of University Medical Centers
NVWA	Netherlands Food and Consumer Product Safety Authority
NWO	Dutch Research Council
QMS	Quality Management System
SAE	Serious Adverse Event
SI	single institution
SOP	Standard Operating Procedure
STZ	Dutch association of Collaborating Top Clinical Hospitals
UMC	University Medical Center
UK	United Kingdom
WMO	Medical Research Involving Human Subjects Act
WoS	Web of Science

Appendices (A-C)

Appendix A

Table 2 Details of evidence used in this study

Interviews
In-depth interviews (*n*=27) with nine inspectors, three employees of the CCMO, five employees of MRECs, and ten staff or board members of hospitals. Some respondents were interviewed multiple times.
An overview of analyzed documents from 2000 to 2018 (if any)
CCMO press releases, annual reports, guidelines, or other publications
IGJ annual reports
IGJ press releases
MRECs (NVMREC) 'Forum'
IGJ presentations to external stakeholders from 2014 to 2018 - Presentation to Board of directors University Medical Centers - Presentation to Board of directors STZ - Presentation at meeting of the Dutch Clinical Research Foundation
Reports on the Propatria study
Press releases of the Dutch Ministry of Health
EU regulation governing clinical trials
Dutch regulation governing clinical trials or medical research
Reviews of EU legislation (EUCTD)
Reviews of Dutch national legislation (WMO)
Public consultation paper "Assessment of the functioning of the 'Clinical Trials Directive' 2001/20/EC" (2009)
Revision of the Clinical Trials Directive. Concept paper submitted for public consultation (2011)
Transcripts of all debates in the Dutch parliament on the regulation of clinical trials
Media reports relating the regulation of clinical trials and incidents
Dutch journals where any reference to clinical trials or medical research were made

Topic lists

Supervisory bodies (IGJ, CCMO, MRECs)
Subject/dimensions:

- Their internal organization, resources, and capacities
- Their working methods: procedures for core regulatory activities, involvement in national and international activities, enforcement powers, and accountability
- Experience with their regulatory activities
- Working relationship with other supervisory bodies or actors: information gathering and flow, coordination, and cooperation activities, if any
- Dealing with external challenges: responses to changes in regulations and incidents; effects on mutual exchange of information, cooperation, and coordination with other supervisory bodies or actors

Staff and board of hospitals
Subject/dimensions:

- Their experiences with the regulatory activities of the IGJ, MRECs and CCMO
- Dealing with external challenges: responses to changes in regulations and incidents; their effects

Table 3 Themes and their related codes

Themes	Codes
Interconnection/interdependence of responsibilities and working relationships among three public supervisory bodies	
Division of roles and responsibilities in the supervision of ongoing trials: problems with diverging interpretations of roles and responsibilities; options to streamline and accelerate the supervision of ongoing trials	Redefining roles and responsibilities; frictions; jurisdiction; tension; conflicts; alignment "supervision of supervision"; information flow; (in)formal consultations; coordination tasks working together in EU working groups; protocol Institutional work: maintenance, creation, coordination
Daily control of safety reports: problems with current method of reporting SAEs; options for improvement	Ambiguity in roles and responsibilities; information flow; workforce; funding; redefining and digitalizing reporting process of SAEs Institutional work: maintenance, creation
IGJ inspections of IITs in hospitals: options for a risk-based approach that adopts different regulatory frameworks depending on the type of supervised hospital (UMC or teaching hospital)	Focus on one or more IITs; working method model; legal framework; duration and scope of inspections; sharing inspection results; stimulating quality assurance and self-regulation of sponsors through the Association of Top Clinical Teaching Hospitals Institutional work: creation, positioning

Appendix B

Topics lists

Topics for guiding interviews with the board of directors and staff members of hospitals regarding their quality management and monitoring/mentoring system

At this particular hospital:
- What approach(es) is/are chosen for a quality management system? Why?
- What are the role and responsibility of the BoD and staff in the development, implementation, and maintenance of a quality management system?
- What is the objective of monitoring/mentoring?
- What is the position of monitors/mentors within the organization?
- What are the tasks, responsibilities, and authorities (competences) of a monitor/mentor?
- Have the monitors been trained and by whom?
- Do monitors/mentors have additional tasks?
- Who bears the costs of monitoring/mentoring?
- How does the process of monitoring/mentoring work?
- How is the available capacity of monitors/mentors distributed among the studies?
- How are studies selected for monitoring/mentoring? Based on risk classification?
- Which documents or parts of a study (informed consent, SAEs, primary endpoints, etc.) are monitored/mentored? Why?
- Is there a standard monitoring plan, SOPs, etc.?
- Are software programs used to support the monitoring/mentoring process?
- What learning experiences have been gained and how have they been dealt with?
- What factors play a crucial role in the monitoring/mentoring process?
- What is the role of their (sub)sector associations regarding quality assurance standards, SOPs, etc.? Is learning from each other supported? Is there an open exchange of data?

Topics for guiding interviews with monitors/mentors and observations of a monitoring/mentoring visit

General:
- Background and career monitor/mentor (education, training)
- Responsibilities and tasks
- Moments of interaction between whom (e.g., staff department, researchers, other monitors/mentors) and about what
- Frequency and average time of monitoring/mentoring visit(s)
- Preparation activities of a monitoring/mentoring visit regarding study file, contact with the researcher, etc.

Conducting a monitoring/mentoring visit:
- Place of monitoring/mentoring
- Researcher present during the (entire) monitoring/mentoring visit
- Building a social relationship with the researcher
- Which documents or parts of a study (informed consent, SAEs, primary endpoints, etc.) are monitored/mentored and for what reason (safety, risk, data validity, etc.)?
- Using a (standard) checklist, templates, SOPs, software programs, etc.
- Documentation of findings including decision-making process of it
- Atmosphere during a monitoring/mentoring visit (relaxed, constructive, open, tense, etc.)

- Relationship between monitor/mentor and researcher: interaction and collaboration
- Facilitating/supporting the learning process of the researcher by the monitor/mentor
- Reporting process
- Follow-up appointments

Additional interview questions:

- Can you tell a special anecdote about a monitoring/mentoring visit? What is the funniest thing you have ever experienced as a monitor?
- If problems arise (incidents/conflicts), how are they resolved?
- If you see an irreparable error (SAE or informed consent), how do you proceed?
- Do you as a monitor/mentor learn from other monitors/mentors? If so, how do you exchange experiences with each other?
- Respond to the following terms: professionalism, authority, expertise, decision-making power.

Online questionnaire

Quality assurance of investigator-initiated studies

Questionnaire on the quality assurance of investigator-initiated studies by the board of directors of Dutch hospitals

1. YOUR SITUATION

Question 1

Which type of hospital do you manage?

- ☐ General hospital
- ☐ Specialized hospital
- ☐ Top clinical hospital (member of the Association of Top Clinical Teaching Hospitals (STZ))
- ☐ University medical center
- ☐ Other, namely _

Question 2

What is your function?

- ☐ Chairman of the board of directors
- ☐ Member of the board of directors
- ☐ Director
- ☐ Dean
- ☐ Other, namely _

Question 3

How many members does your management or board of directors have?

- ☐ 1 member
- ☐ 2 members
- ☐ 3 members
- ☐ 4 members
- ☐ 5 or more members

If Question 2 = Member of the board of directors, then fill in

Question 4

You indicated that you are a member of the board of directors. Which position do you fulfill?

_ _

Question 5

How many years of work experience do you have in this or a similar position?

- ☐ Less than 1 year
- ☐ 1 to 5 years
- ☐ 5 to 10 years
- ☐ More than 10 years

Question 6

How are your medical specialists predominantly employed?

- ☐ In paid employment
- ☐ In a partnership
- ☐ Other, namely _

Question 7
Do researchers initiate studies at your hospital?
☐ Yes *(go to question 8)*
☐ No *(go to 'Finally', question 35)*

2. NUMBERS AND FUNDING

If question 7 = yes, then fill in
Question 8
How many clinical trials were conducted at your facility in 2016, according to your estimation?
The term clinical research has been used as an umbrella term; this also includes investigator-initiated studies.
☐ Less than 10
☐ 10 to 50
☐ 50 to 100
☐ 100 to 150
☐ 150 to 200
☐ 200 to 250
☐ 250 to 300
☐ 300 to 350
☐ 350 to 400
☐ More than 400
☐ I don't know

Explanation of question 9
For the following questions, a distinction has been made between three types of investigator-initiated studies:

A. the studies that are only carried out in your hospital (monocenter),
B. studies that are carried out in a multicenter context in which the hospital is the sponsor and
C. studies that are carried out in a multicenter context in which your hospital is a participating center.

Question 9
How many investigator-initiated studies were conducted in your hospital in 2016, according to your estimation?

Number of studies	A. Monocenter	B. Multicenter as sponsor/client	C. Multicenter as a participating center
Less than 10	☐	☐	☐
10 to 50	☐	☐	☐
50 to 100	☐	☐	☐
100 to 150	☐	☐	☐
150 to 200	☐	☐	☐
200 to 250	☐	☐	☐
250 to 300	☐	☐	☐
300 to 350	☐	☐	☐
350 to 400	☐	☐	☐
More than 400	☐	☐	☐
I don't know	☐	☐	☐

Question 10
Does your hospital make its own financial resources available for conducting investigator-initiated studies?
☐ Yes
☐ No
☐ I don't know

Question 11
How does your hospital receive financial resources for conducting investigator-initiated studies? *(multiple answers possible)*
☐ Independent public organizations (e.g., the Dutch Research Council (NWO) or the Netherlands Organization for Health Research and Development (ZonMw))
☐ Business (including the pharmaceutical industry)
☐ Funds from the European Union or collection box funds
☐ The hospital's friends fund
☐ Other, namely _

3. QUALITY ASSURANCE

Explanation of question 12
Below are a number of questions and statements focused on three topics: vision and policy, your role as part of the board of directors, and the internal supervision of investigator-initiated studies.

Question 12
Has your hospital formulated a vision on clinical research?
The term clinical research has been used as an umbrella term; this also includes investigator-initiated studies.
☐ Yes *(go to question 13)*
☐ No *(to question 14)*
☐ I don't know *(to question 14)*

Explanation of question 13
Quality assurance means ensuring that scientific research is carried out in a responsible manner and that the data is generated, documented (recorded), and reported in accordance with applicable legislation and regulations.

Question 13
The vision on clinical research of your hospital emphasizes the importance of quality assurance of clinical research.
The term clinical research has been used as an umbrella term that covers investigator-initiated studies.
☐ Not applicable at all
☐ Not applicable
☐ Neither not applicable nor applicable
☐ Applicable
☐ Fully applicable
☐ I don't know

Question 14
Has your hospital formulated policy regarding clinical research?
☐ Yes *(continue with question 15)*
☐ No *(go to question 16)*
☐ I don't know *(go to question 16)*

If question 14 = yes, then fill in
Question 15
The clinical research policy in your hospital emphasizes the importance of quality assurance.
☐ Not applicable at all
☐ Not applicable
☐ Neither not applicable nor applicable
☐ Applicable
☐ Fully applicable
☐ I don't know

If question 14 = no, I don't know then fill in
Question 16

Questions	No	Yes	I don't know
a. Do you respond to national or social developments in the field of investigator-initiated studies?	☐	☐	☐
b. Do you respond to regional developments in the field of investigator-initiated studies?	☐	☐	☐
c. Do you set priorities regarding the improvement and safeguarding of your own initiated studies in consultation with stakeholders?	☐	☐	☐
d. Are you supported by a scientific bureau/committee or advisory committee responsible for the coordination and/or execution of quality assurance activities of investigator-initiated studies?	☐	☐	☐

If question 16c = yes, then fill in
Question 17
You indicated that you set priorities regarding the improvement and safeguarding your own initiated studies in consultation with stakeholders.
Which stakeholders do you involve in this? (multiple answers possible)
☐ Management
☐ Clinicians
☐ Healthcare professionals (such as nurses or paramedics)
☐ Clients/patients/subjects

Explanation of question 18
You need to distribute 100 points between the six components. If no points would be allocated to a component, then please enter zero.

Question 18

How much value do you attach to the following quality assurance components of investigator-initiated studies?	Score
a. an improvement culture	
b. a safe learning climate	
c. using information from satisfaction surveys among patients or test subjects	
d. taking corrective action based on adverse events	
e. facilitating investigator-initiated studies	
f. Other, namely _	
Total	100

Question 19

How do you assess yourself in your role as the person with ultimate responsibility or as sponsor/client of investigator-initiated studies with regard to...	Insufficient	Neither insufficient nor sufficient	Sufficient	I don't know
a.... your knowledge	☐	☐	☐	☐
b.... your skills	☐	☐	☐	☐

Explanation of question 20

The following questions are about internal monitoring of investigator-initiated studies.

Question 20

Theses	Not appli-cable at all	Not appli-cable	Neither not appli-cable nor appli-cable	Appli-cable	Fully appli-cable	I don't know
a. Information about the activities of self-initiated studies in your hospital is transparent. *Transparent means the adequacy of the data and operations are clear.*	☐	☐	☐	☐	☐	☐
b. Your hospital can generate internal information and feedback systems for (periodic) information about quality (assurance) of investigator-initiated studies.	☐	☐	☐	☐	☐	☐
c. Your hospital has a data management system to guarantee the quality and safety of the collected data. *A data management system is a software system used to access and retrieve data which are stored in a database.*	☐	☐	☐	☐	☐	☐

Theses	Not appli-cable at all	Not appli-cable	Neither not appli-cable nor appli-cable	Appli-cable	Fully appli-cable	I don't know
d. Internal supervision of the quality assurance of investigator-initiated studies is effective. *Supervision is effective if what is intended is achieved.*	☐	☐	☐	☐	☐	☐

Question 21
How often per year do you receive information about the quality assurance of your own initiated studies for which your hospital is ultimately responsible or the sponsor/client?
☐ Never
☐ Once a year
☐ 2 to 10 times a year
☐ 10 to 20 times a year
☐ More than 20 times a year
☐ I don't know

Question 22
How much time, on average, do you spend per week on quality assurance of investigator-initiated studies?
☐ Less than 1 hour per week
☐ 1 to 2 hours a week
☐ 2 to 4 hours a week
☐ 4 to 8 hours a week
☐ 8 to 12 hours a week
☐ More than 12 hours a week

4. MONITORING AND INTERNAL AUDITING OF INVESTIGATOR-INITIATED STUDIES

Explanation of question 23

Monitoring *is a quality assurance tool aimed at the progress of investigator-initiated studies. Monitoring focuses on:*
- whether the rights and well-being of subjects are protected,
- whether the reported data from the investigation is correct and fully verifiable in source documents, and
- whether the conduct of the study is in accordance with the approved protocol and amendments and with legal requirements, guidelines, and the hospital's own procedures.

Internal auditing *is an instrument aimed at the quality assurance process to check whether the various parties involved in, among other things, investigator-initiated studies have carried out their tasks and responsibilities in accordance with legal requirements, guidelines, and the hospital's own procedures.*

Question 23

Does your hospital carry out the following activities with regard to investigator-initiated studies?	No	Yes	I don't know
a. Monitoring	☐	☐	☐
b. Internal auditing	☐	☐	☐

Question 24

Which standards does your hospital use for monitoring and/or internal auditing? *(multiple answers possible)*	Monitoring	Internal uiting
a. Standards based on laws and regulations	☐	☐
b. Standards drawn up by the trade association (NFU, STZ, NVZ)	☐	☐
c. Standards based on a guideline (such as ICH GCP)	☐	☐
d. Standards drawn up by your own hospital	☐	☐
e. Standards drawn up by the Netherlands Institute for Accreditation of Hospitals (NIAZ)	☐	☐
f. Standards prepared by Joint Commission International (JCI)	☐	☐
g. Other, namely _	☐	☐

Question 25

Does your hospital work with risk classification of investigator-initiated studies?

☐ No
☐ Yes
☐ I don't know

Question 26

On what principle(s) is your system of monitoring and/or internal auditing of investigator- initiated studies based? *(multiple answers possible)*	Monitoring	Internal auditing
a. On the basis of risk (risk classification)	☐	☐
b. On the basis of incidents	☐	☐
c. As a continuous feedback mechanism	☐	☐
d. As a continuous learning process	☐	☐
e. Other, namely _	☐	☐

Question 27

Who carries out monitoring visits and/or internal audits in your hospital? *(multiple answers possible)*	Monitoring	Internal auditing
a. Medical specialists	☐	☐
b. (Research) nurses	☐	☐
c. Data managers	☐	☐
d. Management	☐	☐
e. Qualified professionals *(a professional if with sufficient expertise in conducting research, who does not conduct it themselves)*	☐	☐
f. Other, namely _	☐	☐

Question 28

In your estimation, how many monitors and/or auditors are currently active in your hospital?	Monitoring	Internal auditing
a. Less than 5	☐	☐
b. 5 to 10	☐	☐
c. 10 to 20	☐	☐
d. 20 to 30	☐	☐
e. More than 30	☐	☐
f. I don't know	☐	☐

Question 29

Do the monitors and/or auditors receive support in one of the following ways? *(multiple answers possible)*	Monitoring	Internal auditing
a. Training (e.g., professional development as monitor or internal auditor)	☐	☐
b. Evaluation (e.g., about experiences with monitoring or internal auditing)	☐	☐
c. Neither	☐	☐

Question 30

Do you work with one or more hospitals in the field of monitoring and/or internal auditing of investigator-initiated studies?	Monitoring	Internal auditing
☐ No	☐	☐
☐ No, but we intend to work together within 1 year	☐	☐
☐ Yes	☐	☐

If question 30 (monitoring) = no & question 30 (internal audit) = no, then go to question 35.
If question 30 (monitoring) <> no & question 30 (internal audit) = no, then go to question 31.
If question 30 (monitoring) = no & question 30 (internal audit) <> no, then go to question 31.

Question 31

What is the nature or intention of the (expected) collaboration? *(multiple answers possible)*	Monitoring	Internal auditing
a. Improvement: make the organization work smarter	☐	☐
b. Renewal: discover new possibilities	☐	☐
c. Sharing: intensive mutual coordination	☐	☐
d. Exchange: sustainable exchange of products, services, information, knowledge, and certificates and/or quality marks	☐	☐

Question 32

What type of hospital do you work with or do you want to work with? *(multiple answers possible)*	Monitoring	Internal auditing
a. University medical center in my region	☐	☐
b. University medical center outside of my region	☐	☐
c. Teaching hospital (STZ) in my region	☐	☐
d. Teaching hospital (STZ) outside of my region	☐	☐
e. General hospital in my region	☐	☐
f. General hospital outside of my region	☐	☐
g. Other	☐	☐

Question 33

Have financial agreements been made concerning the collaboration?	Monitoring	Internal auditing
☐ No	☐	☐
☐ Yes	☐	☐

Question 34
Could you please clarify your answer both in terms of monitoring and internal auditing?
- *If so, does the collaboration take place through closed exchanges?*
- *If not, how have financial agreements been made?*

_ _
_ _

5. FINALLY

Question 35
Would you like to participate in a follow-up study: an interview of a maximum of 45 minutes?
☐ No
☐ Yes
In a follow-up question, you will be asked to write down your email address. Your email address will only be used for this purpose: your answers will remain anonymous.

Question 36
Do you have ideas and/or suggestions? We would like to hear them.

_ _

Fill in if question 35 = yes
Question 37
Thank you. You indicated you are willing to participate in a follow-up study. Please enter your email address at which you can be reached below.

_ _

This is the end of the questionnaire. We would like to thank you very much for your participation. If you have any questions in response to this questionnaire, please contact us: [*contact information*]

Table 3. Characteristics of hospitals

	UMC I [2017]	UMC II [2016]	UMC III [2016]	Teaching hospital I [2015–2016]	Teaching hospital II [2018]	Teaching hospital III [2016]	Teaching hospital IV [2018]	Teaching hospital V [2018]
Data collection method	interview staff and observation	interview staff and observation	interview staff and two monitors	interview staff and observation	interview staff	interview staff	interview staff	interview staff
Chosen system	Mentoring, recently started	Monitoring and mentoring	Monitoring	Mentoring, recently started	Monitoring; (re)thinking/ (re) considering the system	Orienting toward a mentoring system	Mentoring	Mentoring
Motivation to start monitoring	Inspection visits and internal research to verify the inspection results	NFU guideline, inspection visits, and Propatria incident	NFU guideline, inspection visits, and Propatria incident	Inspection visits	Inspection visits	Inspection visits; results of other teaching hospitals	Inspection visits	STZ appointments
Link with MREC on approved research proposals	Yes	Yes	Yes	Yes	No, investigators deal with different MRECs	No, building and rolling out a system and a procedure	Yes	No, investigators deal with different MRECs
Selected studies	All WMO research studies (including IITs) except research sponsored by the pharmaceutical industry	All WMO research studies (including IITs) except research sponsored by the pharmaceutical industry	All WMO research studies (including IITs) except research sponsored by the pharmaceutical industry	IITs	IITs	IITs (planned)	IITs	IITs
Monitoring program compulsory or voluntary	Aim compulsory; in start-up phase	Compulsory	Compulsory	Aim: compulsory; in start-up phase	-	Voluntary (planned)	Rethinking the program	Aim: compulsory; in start-up phase
Detailed Description	Two mentors work together to mentor one research study during a central organized mentoring day (peers)	Nine divisions have provided money for central monitoring with which two centrally appointed external monitors are temporarily appointed and paid. In the other three divisions, monitoring is done by self-trained personnel. Research with minimal risk is monitored by a research nurse or BROK*-qualified researcher (mentoring)	Monitors, most with a pharmaceutical background, are a part of a staff department	Peer-to-peer mentoring with two researchers assessing each other's study	Monitoring; (re)thinking/ (re) considering the system	Mentoring (planned). At this moment, no policy, programs, or structures available; building on the experiences of teaching hospital I	Mentoring is done by a research nurse	Mentoring, building on the experiences of teaching hospital I

*BROK: Basic course in regulation and organization for clinical researcher

Table 3. Continued -Characteristics of hospitals

	UMC I [2017]	UMC II [2016]	UMC III [2016]	Teaching hospital I [2015–2016]	Teaching hospital II [2018]	Teaching hospital III [2016]	Teaching hospital IV [2018]	Teaching hospital V [2018]
Qualification requirements for monitors/ mentors	Internal mentors receive brief training from an external partner. Staff member is qualified as a monitor	Low-risk research by a internal monitor. Middle/high-risk research by employees of internal research center; training by their research center	Qualified monitors working in a staff department focusing on research (no additional tasks).	Internal mentors who will receive training in the near future. Staff member is qualified as a monitor	-	Internal mentors (planned). Staff member is qualified as a monitor	Rethinking qualifications; internal mentors received training from an external partner	Internal mentors
Recruitment, managing, and support of monitors/ mentors	Staff department; recruitment by department (obligatory)	Staff department; recruitment by department (obligatory)	Staff department; working with internal monitors	Staff department; recruitment by department (obligatory)	Staff department	Staff department	Staff department	Staff department
Budget by	Departments	Low risk: existing budgets Middle/high risk: temporarily financed by board of directors	Board of directors	Closed stock exchange	Board of directors	Received a grant to start mentoring	-	Closed stock exchange
Written procedures	Yes	Yes	Yes	STZ procedures adjusted to their own situation	STZ procedures adjusted to their own situation	STZ procedures adjusted to their own situation (planned)	STZ procedures adjusted to their own situation	STZ procedures adjusted to their own situation
Based on NFU risk classification	Yes, since 2016	Yes, since NFU guidelines were published in 2002	Yes	Yes	Yes	-	Yes	Yes
Organizing meetings for research stakeholders	Lunch meetings for mentors during a mentoring day to exchange experiences; planning a symposium for peers	Peer mentors' meeting to exchange experiences led by (external) monitors	(Lunch) meetings with researchers	Yes	Yes	Yes	Yes	Yes

Reference list (example)

Version 9: April 11, 2014	
Quality control of investigator-initiated studies	
(Monitoring)	
Monitor(s):	
Date:	
Study acronym:	
MREC nr.: / Local assessment	
Executive researcher:	
Lead researcher:	
Documents to be monitored	**agreed?**

GENERAL STUDY INFORMATION					
1. Protocol & amendments:	**Yes**	**No**	**N/A***	**NTF?****	**Com-ments**
Has the study protocol been approved by the Medical Research Ethics Committee (MREC) or a competent authority?					
Is the latest version of the protocol that has been approved by the MREC present?					
Is the protocol signature page provided with the date and signature?					
Signed protocol amendments present (version corresponds to last approved version by the MREC)					
Description of task Data Safety Monitoring Board (DSMB) present? The protocol must state how the DSMB is structured, what members (disciplines) and what their duties are within that study.					
DSMB reports present?					
2. Investigators Brochure	**Yes**	**No**	**N/A**	**NTF?**	**Com-ments**
Relevant and updated scientific information regarding the research product available?					
Most recent version present and seen/approved by MREC?					
3. Serious adverse events (SAEs)/SUSARs@	**Yes**	**No**	**N/A**	**NTF?**	**Com-ments**
SAEs and associated reports were announced by the investigator within 24 hours.					
SAEs are defined - Check on 100% of reported SAEs					

Standard operating procedure (SOP) "(Serious) Adverse Events" present					
4. Insurance	**Yes**	**No**	**N/A**	**NTF?**	**Com-ments**
Insurance certificate of the test subject's insurance available?					
Insurance certificate of the hospital's liability insurance available?					
MREC					
5. Medical Ethical Review	**Yes**	**No**	**N/A**	**NTF?**	**Com-ments**
MREC approval: dated, written positive judgment from the assessing MREC					
Local practicability statement: written positive assessment of the assessment for local practicability, signed by the Manager of the care unit					
Letter of approval from the Board of Directors to start.					
Amendment approval by the MREC***					
Annual report to the MREC					
TRIAL PARTICIPANT INFORMATION					
6. Patient information letter and Informed Consent	**Yes**	**No**	**N/A**	**NTF?**	**Com-ments**
SOP 'Informed consent procedure' present					
Most recent Patient information letter and Informed consent present					
Patient information letter & Informed consent forms (1 document) are provided with a unique version number and date that corresponds to the version approved by the MREC. Correct version available?					
Patient information letter & Informed Consent forms from **all** participating patients printed on hospital stationery					
Date, name, and signature are placed by the patient/legal representative at a time prior to participation in the study (check all participants). In the case of children: signature of both parents or legal representative(s). For the signature of one parent, explain why the signature of the other parent is missing. (check 100% of participants in study)					

The researcher has placed the date, name, and signature at a time prior to participation in the study					
It is documented that the patient has had sufficient time for consideration before signing informed consent					
7. Patient inclusion	**Yes**	**No**	**N/A**	**NTF?**	**Com-ments**
Patient screening log: list of test subjects who have been screened for possible participation in the study and the reason why they have or have not participated including name and birthdate***					
Patient inclusion log: list of inclusion of test subjects including a clinical trial number/subject number. Log present?					
Patient identification list (list of codes and test subject identification) such as:					
• name					
• PIN number					
• gender					
• Informed Consent date					
Drug Accountability Form (medication lists of included patients) including: (this form is often at the pharmacy. Check for presence)					
• Study medication number					
• Dosage					
• Name of operator/name of medication issue					
• Amount of returned medication***					
• Amount destroyed if applicable					
SITE INFORMATION					
8. Curriculum Vitae:	**Yes**	**No**	**N/A**	**NTF?**	**Com-ments**
Up to date curriculum vitae and/or other relevant documents to prove the qualifications of the responsible executive and researcher with a signature (valid 2 yrs)					
CV is provided with BIG registration number (in NL)					
CVs are all provided with the signature and date of the person concerned (and therefore not of the researcher! Researcher is not allowed to sign the CV of others)					

9. Delegation log	Yes	No	N/A	NTF?	Com-ments
List of delegated tasks and associated signatures and initials of all personnel involved who are authorized to record data in the context of the study/to perform tasks in the context of the study					
Personnel named on delegation log are authorized to perform said tasks (according to CV)					
10. Laboratory	**Yes**	**No**	**N/A**	**NTF?**	**Com-ments**
Normal values present***					
Certificate: certification or accreditation or established internal quality control, to support the suitability of the facilities to implement the provisions and the reliability of the results and is this provided with the date and signature of the competent person?***					
There is an overview of the required lab materials and the location of archiving of lab materials***					
RESEARCH PRODUCT AND STUDY MATERIAL					
11. Investigational Medicinal Product File (IMPD) or SmPC (Summary of Product Characteristics):	**Yes**	**No**	**N/A**	**NTF?**	**Com-ments**
Are the clinical and non-clinical data of the research product relevant to the study present?***					
12. Data processing & storage					
Investigator Site File (ISF) is up to date: all documents are present according to specified content page					
Documents/USB/CDs, etc., with information from which the patient could be identified are stored in lockable rooms					
A patient identification code is used in all analysis files. In other words, everything that appears in the Case Report Form or for external analysis has been rendered anonymous or coded					
With electronic data processing there is always a backup present (L-disk) Method of backup is described***					

If data has been edited, there is the option to compare the original data and observations with the edited data (version management files using date)					
Data can be accessed with password					
SOP 'Data processing and storage' is available					
CORRESPONDENCE AND CONTRACT					
13. Agreement	**Yes**	**No**	**N/A**	**NTF?**	**Com-ments**
Financial agreement is signed by both the principal investigator and the chairman of the Board of Directors***					
Trial agreement: signed agreements between parties involved in the hospital, including clinical pharmacy, clinical chemistry, radiology, etc. is present and provided with the necessary signatures					
OTHERS					
14. Education	**Yes**	**No**	**N/A**	**NTF?**	**Com-ments**
The executive researcher has followed a certified GCP training or the BROK course (certificate) and this certificate is no older than 4 years					
Involved personnel have followed a GCP course (with certificate) in the past 4 years					
Principal investigator has followed the GCP course or the BROK course (certificate)					
Conducted study-specific training (with certificate of the persons concerned)					
15. Endpoints	**Yes**	**No**	**N/A**	**NTF?**	**Com-ments**
Endpoints are laid down in a protocol					
A specific mention of the primary endpoints and any secondary endpoints that will be measured during the study					
Check of the primary endpoints mentioned in the protocol in 100% of the participating patients					

16. Miscellaneous					
Monitor reports present?					
Are all SOPs of study actions filed in the ISF? (For example, SOP IC collection, SOP randomization, SOP blood collection)					

*Na : not applicable
**NTF: note to file
*** = If applicable
@SUSAR = Suspected Unexpected Serious Adverse Reaction

Appendix C

Table A1 Overview of bibliometric indicators per hospital (and hospital unit) during the time periods considered

Indicator	Dimension	Definition
P	Output	Number of papers (normal articles and reviews) published in journals processed for the WoS
MCS	Impact	Average number of citations per publication, excluding self-citations
MNCS[abc]	Impact	Mean normalized citation score (in comparison with other hospitals)
MNJS	Journal Impact	Mean normalized journal score
PP (top 10%)	Impact	Percentage of papers that are among the 10% most frequently cited of all similar papers during the time period considered
PP (uncited)	Overall	Percentage of articles not cited during the time period considered, excluding self-citations
PP (self-citations)	Overall	Percentage of self-citations; a self-citation is defined as a citation in which the citing and cited paper have at least one author in common (first author or co-author)

[a] If the MNCS is higher (or lower) than 1, then on average, the output of the domain is cited more often (or less often) than an "average" publication in the research area in which the domain is active. Like the MNCS, the MNJS indicates the authors' choice of journal: when the MNJS is far above 1, the author publishes in journals with a high impact in their research specialism, while a score below 1 indicates that the journal has a somewhat lower standing in that specialism.

[b] The impact indicators MNCS, MNJS, and PP (top 10%) are based on a new method of normalization. While previously normalization was based on WoS Journal Subject categories, we have now moved toward a method in which science is grouped into roughly 4,000 clusters, allowing for a like-with-like comparison in which the impact is compared on a much lower scale than the WoS JSCs, which often contain sub-specialisms with rather divergent citation cultures, leading to inaccurate densities in citation traffic. This created an unfair situation, which the current methodology resolves (Traag et al., 2019).

[c] In the bibliometric analysis applied for all eight UMCs and 28 non-academic hospitals, we have added one additional year to the overall citation window for the set of publications. At the time of the study, we selected the papers published in the 2009-2018 period. While 2019 was available at that moment, including 2019 publications would mean providing only one year of the citation window to the set of 2019 publications. This means that the citation numbers would be biased within that year toward the ones published earliest in the year, with the first-quarter publications having a clear citation advantage over the publications published later in the year. This would have a disproportional influence on the overall citation analysis, and that is why we decided in the CWTS methodology to always exclude the papers from the final year of a time period, but include that year for citation analysis of the previous years.

Table A2 Details of document analysis

Overview of documents analyzed
- Letters to Parliament and documents from the Ministry of Health
- ZonMw's website, letters and reports related to the TopCare program
- Objectives and results of the domains and the projects, such as proposals and reports from the two TopCare non-academic hospitals
- Developments in the field, including documents from the Association of Top Clinical Teaching Hospitals (STZ), the Netherlands Federation of University Medical Centers (NFU), and advisory bodies
- Media reports related to the TopCare program
- International and Dutch journals referencing the TopCare program
- Publications evaluating the Collaborations for Leadership in Applied Health Research and Care (CLAHRC)

Table A3 Themes and their related codes (interviews)

Themes	Codes
The relationship between a specific domain and the focus of the TopCare hospital: in a specific domain; scientists are committed to the quality of life of patients, which attracts more of these patients to the hospital and influences its focus; this relationship can impact the strategic value of the hospital	Organizational boundary work: identity [a] Enhancing hospitals' value proposition
High volume of patients in TopCare hospitals to create a new or recognizable and valuable position	Organizational boundary work: identity [a] Enhancing hospitals' value proposition
Using their expertise within a domain to create a new position or enhance their current position	Organizational boundary work: identity [a] Enhancing hospitals' value proposition
Unique history of a domain to create a new position or enhance their current position (negative impact: past conflicts may still influence collaboration in the present; positive impact: having a long history within a domain)	Organizational boundary work: identity [a] Enhancing hospitals' value proposition
Using program funding to enhance the hospitals' research infrastructure	Organizational boundary work: competence [a] Enhancing research infrastructures
Finding alignments across domains within hospital and research networks in order to share and learn	Organizational boundary work: competence [b] Finding alignments within hospitals and research networks
Expanding national and international research networks to share and learn within a domain	Organizational boundary work: competence [b] Finding alignments within hospitals and research networks
TopCare hospital became interlocutor to enhance or find and mobilize a new strategic academic partner	Organizational boundary work: power [a] Enhancing the relationship with or finding and mobilizing strategic academic partners
Board of directors and administrators of the two TopCare hospitals work together to learn from each other	Organizational boundary work: power [b] Aligning with the board of directors and administrators of the TopCare hospitals

Themes	Codes
The person who is ultimately responsible within a hospital's strategic domain focus for specialized treatments that can only be carried out by a highly qualified team of experts and in specialized facilities	Boundary spanner: ultimately responsible for a highly qualified team of experts and specialized facilities within the hospital's strategic domain focus Organizational boundary work: identity [a] Enhancing hospitals' value proposition
The person who is a leading scientist in a non-academic hospital and the driving force in the collaboration	Boundary spanner: leading scientist Organizational boundary work: competence [b] Finding alignments within hospitals and research networks
The key figure is often a professor who has a double affiliation (in a non-academic hospital and a UMC) and orchestrates the engagements within these hospitals	Boundary spanner: double affiliation Organizational boundary work: power [a] Enhancing the relationship with or finding and mobilizing strategic academic partners

Table A4 Types of collaboration on publications between UMCs and non-academic hospitals in the Netherlands

	2009-2018/2019					
	Total number of publications					Joint publication of UMC and non-academic hospital
Types of collaboration on publications	UMCs (n=8)	%	Non-academic hospitals (n=28)	%	Total	
Single institution (SI)	27592	18%	1503	8%	29095 (20%)	
National collaboration (NC)	42557	28%	10880	60%	53436 (31%)	8943
International collaboration (IC)	82540	54%	5896	32%	88435 (52%)	3874
Total	152688	100%	18279	100%	170967 (100%)	12816

- UMCs produce 18 times (=27592/1503) more SI, four times (=42557/10880) more NC, and 14 times (82540/5896) more IC publications than non-academic hospitals.
- Of all publications, 89% (=152688/170967) are attributed to UMCs and 11% (18279/170967) to non-academic hospitals.
- Joint publications in national collaboration: 82% (=8943/10880) non-academic hospitals and 21% (=8943/42557) UMCs.
- Joint international publications: 66% (=3874/5896) non-academic hospitals and 5% (=3874/82540) UMCs.
- Joint publications: 70% (=12816/18279) non-academic hospitals and 8% (=12816/152688) UMCs.

– Relationship between joint publications and total publications in each type of collaboration: 17% (=8943/53436) national collaboration and 4% (=3874/88435) international collaboration.

Table A5 Number of publications in the two periods (in %)

	2009-2012/2013				2014-2017/2018			
	UMCs	%	Non-academic hospitals	%	UMCs	%	Non-academic hospitals	%
Single institution	11204	22%	704	11%	11085	16%	559	7%
National collaboration	15468	30%	4060	63%	18087	26%	4556	57%
International collaboration	24133	48%	1656	26%	39493	58%	2908	36%
Total	50805	100 %	6420	100%	68665	100 %	8022	100 %

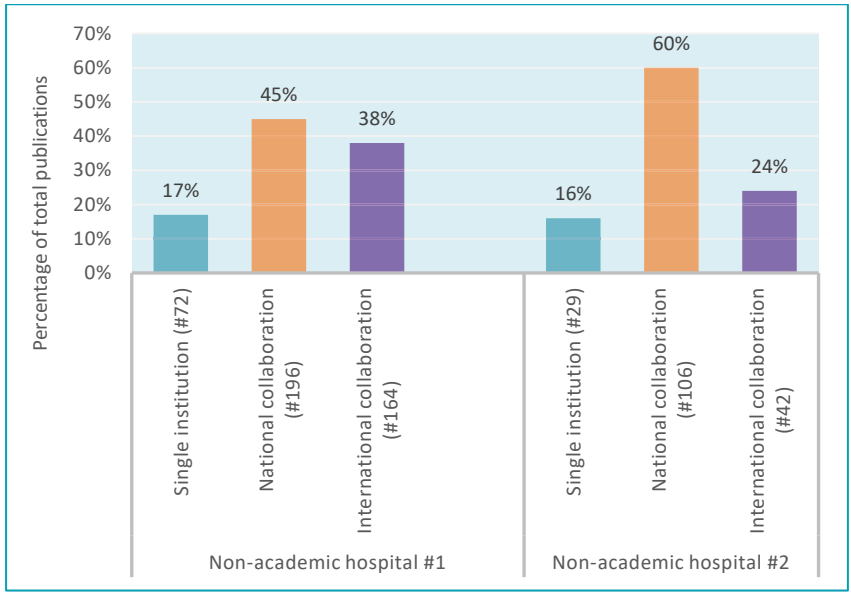
Note: The numbers in Table A5 cannot be compared with the totals in Table A4 because the publication year
2013 is missing in the trend analysis.

Table A6 MNJS

	2009-2018/2019				2009-2012/2013				2014-2017/2018			
	UMCs	#	Non-academic hospitals	#	UMCs	#	Non-academic hospitals	#	UMCs	#	Non-academic hospitals	#
SI	1.23	27592	0.91	1503	1.29	11204	0.95	704	1.22	11085	0.90	559
NC	1.24	42557	1.25	10880	1.30	15468	1.33	4060	1.21	18087	1.21	4556
IC	1.78	82450	1.93	5896	1.82	24133	1.95	1656	1.76	39493	1.96	2908

The MNJS indicates the authors' choice of journal: when the MNJS is far above 1, the author publishes in journals with a high impact in their research specialism, while a score below 1 indicates that the journal has a somewhat lower standing in that specialism.
SI: Single institution, NC: National collaboration, IC: International collaboration
#: Total number of publications

Figure A1 Types of collaboration involving TopCare hospitals #1 and #2 between 2010 and 2016



#: Total number of publications

Table A7 MNCS of the four domains in the TopCare program during the period 2010-2016

		MNCS	Total number of publications
Non-academic hospital #1	Single institution	0.94	72
	National collaboration	1.37	196
	International collaboration	3.44	164
Non-academic hospital #2	Single institution	1.68	29
	National collaboration	1.64	106
	International collaboration	5.85	42

Summary

This dissertation focuses on the governance[25] of medical research in the Netherlands. In any research involving human participants, it is important to weigh two crucial values against each other: the need to protect research participants and the need to safeguard the integrity of research results with impact on society. These key ethical and scientific values are beyond dispute and form the bedrock of all the laws, regulations and standards that govern medical research and its supervision. Some of these frameworks were created after the atrocious medical experiments on humans in the Second World War and are laid down in international treaties.

Ensuring these key values is anything but straightforward in practice, particularly because the landscape of medical research in the Netherlands is constantly evolving. In recent years, the legal landscape has been further harmonized due to the introduction of various European directives and regulations. In addition, research is now increasingly being carried out in non-academic teaching hospitals (in addition to the university medical centres or UMCs where it traditionally took place) and in multiple centres simultaneously. These dynamics mean that actors have to adapt, for example by aligning the Dutch supervision and review system with the new European Union (EU) requirements, or by developing a monitoring system in hospitals. To identify these adaptations, I use the concept of 'institutional work', which includes activities that actors undertake to create, maintain or disrupt institutional structures.

Empirically, this study aims to understand how public and private actors interpret key ethical and scientific values and translate them into actions to protect participants and safeguard scientific integrity. These actors

[25]In this dissertation, I explore the governance actions of actors by applying institutional theories as my methods of analysis. I use the following broad definition of governance: 'the process of directing society and the economy ("how") through collective action and in accordance with common goals ("what")' (Torfing et al., 2012, in Ansell & Torfing, 2022, p. 3). A governance approach is based on the idea that various actors involved monitor the quality of medical research and that further institutional work needs to be done in all kinds of practices of review and supervision to ensure this quality. This approach fits the chosen domain of medical research in which multiple actors are involved in review and supervision.

increasingly share responsibility for the proper functioning of governance practices. I mainly used qualitative research methods to collect the data and focused on collecting stories from relevant actors about how they interpret their beliefs and practices, as well as my own observations of monitoring and supervision practices.

Conceptually, this study contributes to academic and pollical-administrative debates on future-proofing policies and practices in medical research: from supervision, review, and conduct to the publication of research. By demonstrating the importance of a governance approach—alongside legal and institutional approaches—it becomes clear how challenges in medical research can be addressed; such an integrated approach is essential to protect and safeguard ethical and scientific key values. By making the institutional work of interdependent (supervisory) actors visible around three interconnected governance mechanisms – rules, room and responsibilities – it becomes clear how actors can develop a certain degree of resilience. This resilience offers them the room to deal flexibly with changes (dynamics) while at the same time complying with rules and responsibilities that are essential for protecting and safeguarding key values or, conversely, for balancing these values against one another when they conflict.

Medical research in the Netherlands involves a complex playing field that includes research participants, Medical Research Ethics Committees (MRECs), the Central Committee on Research Involving Human Subjects (CCMO), sponsors (i.e. those who commission or are responsible for the research) and the Health and Youth Care Inspectorate (IGJ). This playing field is regulated mainly by the Medical Research Involving Human Subjects Act (WMO), which has been in force since 1999 and offers protection to research participants who take part in research. The regional MRECs are often linked to one or more hospitals. The CCMO acts as a review committee in specific cases. The review committees have the task of assessing and monitoring the ethical and scientific values of research proposals. The CCMO has also been assigned other tasks under the WMO, such as drawing up guidelines for assessing research and accrediting and supervising MRECs. Sponsors of medical research have a specific responsibility to protect participants. Whether it concerns research funded by the pharmaceutical industry or initiated by

researchers themselves (known as investigator-initiated trials or IITs) in hospitals. The regulations require that all actors involved adhere to the same rules, despite their possible unequal situations, i.e. that pharmaceutical companies have a range of experts and financial resources to ensure compliance with legal requirements, whereas these resources are less available in the case of IITs. The Inspectorate is responsible for monitoring ongoing medical research.

The **research question** focuses on understanding the institutional work that public and private actors undertake to address dynamic challenges within the multilevel governance structure of medical research and public supervision. The aim of the study is to expand our understanding of institutional work undertaken by various actors to effectively respond to the ever-changing challenges within different practices. More specifically, the study analyses governance at the following levels within the domain of medical research:

- the effects of EU harmonization policy on public supervision of clinical trials;
- the challenges of public supervision of ongoing clinical trials;
- ensuring data quality in investigator-initiated trials in Dutch hospitals;
- the impact of research collaboration on research output in Dutch hospitals and the initiation and improvement of productive research collaboration in Dutch TopCare hospitals.

Each of these questions has been answered in an empirical chapter and has been published as an academic article.

Chapter 2 focuses on the impact of EU harmonization policy on public supervision of clinical trials. The EU Clinical Trials Directive (CTD) and the EU Clinical Trials Regulation (CTR) aim to harmonize Good Clinical Practice (GCP) of clinical trials across all Member States. Using the Netherlands as a case study, this study analyses how endeavours to implement the CTD set in motion a dynamic process of institutional change and institutional work. This process led to significant differences between policy and actual practice; it is therefore important to learn more about the implementation of harmonization policies.

For this study, interviews were conducted with various stakeholders and Dutch and international supervisory bodies, and observations carried out during IGJ inspection visits.

The study reveals that Dutch legislation created a new governance layer in an already layered legislative framework. This was because the Dutch legislature chose to retain the existing Dutch system of review and supervision as much as possible when implementing the CTD. In the Netherlands, there is no single competent authority responsible for review. As a result, the tasks proposed in the CTD had to be divided among the most important players in public supervision: the IGJ, the CCMO, the MRECs, the Ministry of Health, Welfare and Sport and the Medicines Evaluation Board. Furthermore, unlike the EU regulatory system, the review of ethical values and the review of scientific quality are integrated in the Dutch system.

In the Netherlands, the choice was made to add new rules to existing regulations (also referred to as 'layering ' in institutional theory). This resulted in a complex and fragmented organizational structure in public supervision, leading in turn to institutional work by actors, which then triggered further incremental institutional change. The new division of responsibilities led to overlapping roles in the supervision of ongoing trials, resulting in ambiguity between the IGJ and MRECs. An additional observation is that the IGJ has limited supervision and enforcement powers over entities such as pharmaceutical companies or Contract Research Organisations (CROs) that operate in an international context. For example, it is unclear whether the sponsor or CRO of an international multicentre trial is obliged to respond to the findings of a national inspection when it is trying to comply with multiple sets of regulations and is required to keep its internal protocols consistent.

This study shows that harmonization processes can create dynamic cycles between institutional change and institutional work, leading to significant differences in the way EU GCP rules are translated into Member States' practices. The implementation of harmonization policies should be carefully monitored to avoid unintended consequences that are counterproductive to the aim of harmonization: ensuring both the protection of participants and the reliability of the data obtained.

Chapter 3 examines how agencies involved in supervising ongoing trials have responded to the external challenges of the past two decades, such as EU regulatory harmonization and incidents. In addition, it focuses on how these agencies perform institutional work to maintain, restore or improve the Dutch regulatory regime. This study analyses international and national regulatory documents and interviews with various actors, including public supervision agencies and hospital staff and boards of directors.

In the Netherlands, EU harmonization directed at centralizing and coordinating the regulatory regime for good clinical trial practice in Member States has paradoxically led to further fragmentation. The resulting ambiguity and inefficiency remained largely unresolved until a serious incident in 2008 became a catalyst for change. The incident concerned the Propatria trial in a university hospital, in which the treatment under investigation led to more deaths among patients administrated that treatment than among those administrated the placebo. This incident led to several changes in the institutional design of the governance of medical research.

First, the division of responsibilities between the supervisory authorities CCMO and IGJ was clarified by the Ministry of Health, Welfare and Sport. The IGJ and the CCMO were forced to collaborate during the investigation into the Propatria study and this led, over time, to their being better able to handle their responsibilities and coordinate their supervisory tasks. Second, the WMO was amended in 2015. Reporting of Serious Adverse Events (SAEs) to MRECs became mandatory for all studies governed by the WMO, to ensure the safety of participants. MRECs faced financial constraints, however, which meant that timely review of protocols remained their primary focus, limiting their ability to adapt to these external challenges. Third, the Ministry of Health, Welfare and Sport assigned a new responsibility to the CCMO: annual reporting on the number of SAEs and the consequences for the safety of participants. In response, the CCMO developed a digital tool to facilitate SAE reporting. Fourth, the Propatria incident led the IGJ to address hospital boards of directors about their role as sponsors of IITs. This also clarified their associated supervision responsibilities for ongoing research conducted within their organizations, as described in the WMO. The IGJ pointed out to boards of directors a recurring issue in these inspections: the need to establish a

comprehensive quality system, encompassing auditing and monitoring processes. In addition, the involvement of an actor outside the regulatory framework – the association of Collaborating Top Clinical Hospitals (STZ) – became important in tightening up the supervision of ongoing research. The STZ developed standard operating procedures to complement quality assurance manuals for the affiliated teaching hospitals and facilitated the exchange of lessons learned and best practices.

This study concludes that public supervision of ongoing trials in the Netherlands is fragmented because the responsibilities and resources are unevenly distributed between the relevant actors. In countries with review and supervision systems that, like the system in the Netherlands, differ from the EU mainstream, public supervision bodies must do a great deal of institutional work to align with new EU regulations while safeguarding their traditional regulatory mechanisms that ensure human safety. However, national regulatory traditions also offer new opportunities to improve quality assurance for clinical trials.

Chapter 4 investigates the complexity of regulations governing IITs. This complexity places a great burden on hospitals in terms of compliance, documentation and training of investigators. Many hospitals therefore seek to alleviate regulatory pressures by instituting an alternative quality management system (QMS). To investigate how QMSs for IITs in Dutch hospitals are organized, we adopted the theoretical concepts of 'mentoring ' and 'monitoring'.

In clinical practice and international guidelines, monitoring is seen as the standard approach to quality assurance for ongoing trials. Hospitals, however, have implemented monitoring programmes that resemble mentoring. The contrast between these two approaches is less pronounced in practice, as both combine elements of compliance and feedback for learning in practice. Monitors and mentors both play a facilitating role in promoting responsible research behaviour and interpreting regulations. In a monitoring environment, however, learning is one-way, from monitor to researcher; whereas mentoring focuses on mutual support and learning, with mentor and researcher often switching roles flexibly. Another difference is that while

monitoring focuses on a centrally managed programme for the assessment of research practices, in mentoring this is decentralized and horizontal. Monitoring leads to the establishment of rules that researchers must adhere to, whereas mentoring focuses more on providing peer feedback. For hospitals, mentoring is attractive because it initiates discussions between researchers about the trade-off between the ethical and methodological requirements of research, thus helping to internalize the relevant standards.

To address issues in any system, the authority of the board of directors and their relationship with staff members are crucial. Boards of directors are increasingly embracing their responsibility for the QMS in IITs. The investigation into the Propatria incident and subsequent inspection visits emphasized the need for improved quality management to ensure participant safety and methodological quality during trials. These developments, along with facilitatory support from the STZ, opened avenues for experimenting with new mentoring practices. Hospitals offered mentors, monitors and researchers a setting and environment conducive to learning. This included providing practical support to GCP-qualified researchers in aligning their research procedures with legal requirements. Consequently, both monitoring and mentoring became integral components of QMSs within teaching hospitals and UMCs. The boards of directors had delegated responsibility for implementing these systems to staff departments. The staff departments thus became responsible and accountable for quality control, improvement and assurance of IITs , while the boards of directors, as sponsors, retained overall responsibility.

Chapter 5 delves into the dynamics of research collaboration. In the Netherlands, UMCs bear primary responsibility for conducting medical research and delivering highly specialized care. The TopCare programme was a policy experiment in which three non-academic teaching hospitals received funding from the Ministry of Health, Welfare and Sport to also conduct medical research and deliver highly specialized care in specific domains. This study investigates research collaboration outcomes for all Dutch UMCs and, specifically, in the four domains of two of the non-academic teaching hospitals that participated in the TopCare programme. Additionally, this study explores the organizational boundary work performed by the TopCare

hospitals to foster productive research collaboration. Here, we consider boundary work as a specific type of institutional work that involves efforts to create, maintain or undermine boundaries between organizations or domains. A mixed quantitative and qualitative approach was used for this study.

The quantitative analysis shows that, over the period of study, international collaboration increased among all hospitals while national collaboration and research performed by one hospital declined slightly. Collaborative efforts correlated with higher impact scores, and international collaboration scored higher than national collaboration. Sixty percent of all non-academic teaching hospitals' publications were produced in collaboration with UMCs , while almost 30% of the UMCs' publications were the result of such collaboration. Non-academic teaching hospitals showed a higher degree of collaboration with the geographically closest UMC, whereas TopCare hospitals prioritized expertise over geographical proximity within their specialized domains.

The boundary work of the TopCare hospitals includes aligning research activities with the organizational identity, bolstering the research infrastructure, and finding and mobilizing strategic partnerships with academic partners. These efforts were aimed at establishing the relevant hospital's credibility and attractiveness as collaboration partners. In addition, this boundary work reveals a dual dynamic in that it both opened and safeguarded boundaries. On the one hand, the hospitals concerned cemented their collaborative position and improved or reinforced scientific value in research collaborations with academia. On the other, they did not accomplish the underlying objective of the short-term TopCare programme: to establish structural funding for highly specialized care and medical research in non-academic teaching hospitals.

In short, research collaboration between non-academic teaching hospitals and UMCs, particularly where this also involves international collaboration, pays off in terms of publications and impact. The TopCare hospitals used the programme's resources to perform boundary work aimed at becoming an attractive and credible collaboration partner for academia. Local factors such

as research history , strategic domain focus, in-house expertise, patient flows, infrastructure and network relations influenced collaboration dynamics within TopCare hospitals and between them and UMCs.

Chapter 6 highlights the main themes of this research. The landscape of medical research is continuously shaped by a multitude of dynamic developments, both external and internal. These dynamics resonate at all levels of governance within medical research. When new challenges arise, actors feel a pressing need for recalibration and repair work and constantly seek pragmatic solutions to activate, articulate and ensure key ethical and scientific values. The intentions underlying various regulations, rooted in key values, can thus serve as a moral compass for actors in this field.

In the realm of governance of medical research, it is imperative for the relevant actors to collaborate. This has been especially true in the Dutch context, where multiple actors are also engaged in review and supervision. It requires constant work from the actors to achieve this coordination. This dissertation also shows that while this work is reasonably successful in the preliminary review of research proposals, monitoring a trial during implementation still presents challenges.

In addition, the governance system of medical research has been subject to a complex and fragmented regulatory framework resulting from historical developments, such as the numerous local MRECs operating in the periphery. Such fragmentation has led to dependencies on resources and the actions of and interactions with other levels, affecting the accomplishment of system goals and tasks. This has made close coordination, alignment and collaboration among actors across all levels more necessary in the Netherlands than elsewhere in the EU.

Institutional work is an essential part of various governance practices in effectively addressing dynamic developments. This study shows that actors' institutional work revolves around three interconnected governance mechanisms: rules, room and responsibilities, aimed at safeguarding ethical and scientific key values. 'Rules' encompasses laws, directives, regulations, guidelines and standards that must be adhered to. 'Room' refers to the

flexibility and autonomy that actors need to interpret and safeguard key values in specific practices within those rules. ‘Responsibilities’ entails allocating tasks and duties among different actors, which can lead to a high degree of interdependence in task execution in medical research. By using all three governance mechanisms coherently, actors can establish a resilient governance framework capable of addressing challenges and safeguarding the scientific integrity and ethics of medical research.

'Resilience' is defined as the capacity to prepare for, respond to, or recover from unforeseen problems or disruptions while safeguarding key values. In the pursuit of resilience, actors in the supervision and review system need to collaborate effectively and perform institutional work to foster an optimal balance between rules, room and responsibilities. This involves providing actors with both structure and flexibility in responding to dynamic challenges. Achieving this balance optimizes the actualization of key values. Conversely, an imbalance between rules, room and responsibilities may compromise or impede the safeguarding of these values. This 4R model (*rules , room, responsibility, resilience*) can be instrumental in diagnosing whether various governance mechanisms are balanced among interdependent actors.

At present, the WMO’s authority has been weakened by the enactment of the EU CTR. Certain provisions of the WMO have been declared inapplicable, with direct reference to EU legislation. The EU now plays and is expected to continue playing a substantial role in regulating medical research involving human participants, as part of its efforts to harmonize rules and regulations. In light of these efforts, it is imperative to consider how best to future-proof the Dutch supervision and review system. In doing so, it is important to keep an eye on the relationship between the four Rs, especially as EU law tends to stress 'rules' over 'room'.

The fourth legislative evaluation of the WMO, of which I am a co-author, outlines several recommendations to future-proof the Dutch system. This evaluation proposes solutions to the problem of the CCMO’s dual role, i.e. supervising MREC activities on the one hand and standardizing these activities through guidelines and supporting the MRECs on the other. One solution is to restructure the responsibilities of the CCMO by ending its supervisory

function and transferring this responsibility to the IGJ. This would strengthen the coordinating role of the CCMO and provide it with the necessary institutional room to promote and organize collaboration within the review system.

The legislative evaluation also addresses the challenges that EU regulation and harmonization pose for researchers conducting IITs. Such studies face significant challenges because, compared to pharmaceutical companies, they have limited resources and support at their disposal. Despite these challenges (strict regulations and defined responsibilities), IITs are often of interest to society, as they are driven by clinical imperatives rather than commercial interests. However, complex and detailed requirements, such as those imposed by EU rules and regulations, can also serve as impediments and influence the type of research being conducted. Important topics for legislative evaluation include formulating a vision regarding IITs by such entities as the STZ, the NFU and hospitals, identifying researchers' support requisites, and facilitating IITs within hospital settings. In other words, institutional arrangements that ensure the viability of IITs deserve full attention in the forthcoming evaluations.

To conclude, responding effectively to evolving circumstances in medical research necessitates the integration of three governance mechanisms, i.e. rules, room and responsibilities. These mechanisms collectively ensure that actors within each governance practice learn, improvise and adapt while upholding key ethical and scientific values. Maintaining the integrity and reliability of scientific endeavour amidst dynamic challenges and opportunities requires balancing scientific goals with ethical values, such as minimizing risks to research participants and ensuring informed consent. The synergy of rules, room and responsibilities empowers actors to navigate the complexities inherent in medical research, safeguarding the resilience needed to promote key ethical and scientific values.

Samenvatting

Dit proefschrift richt zich op de governance[26] (sturingsprocessen) van medisch-wetenschappelijk onderzoek in Nederland. In elk onderzoek met menselijke deelnemers is het van belang om twee cruciale waarden tegen elkaar af te wegen: de noodzaak om deelnemers aan onderzoeksprojecten te beschermen en de noodzaak om integere onderzoeksresultaten met een maatschappelijke impact te waarborgen. Deze ethische en wetenschappelijke kernwaarden staan buiten kijf en vormen de basiskaders van alle wetten, regels en normen die het medisch-wetenschappelijk onderzoek en het toezicht daarop regelen. Deze kaders zijn mede ontstaan na de afschuwelijke medische experimenten op mensen in de Tweede Wereldoorlog en zijn vastgelegd in internationale verdragen.

Het waarborgen van deze kernwaarden is in de praktijk allesbehalve eenvoudig, met name omdat het medisch-wetenschappelijk landschap in Nederland voortdurend verandert. In de afgelopen jaren is het juridisch landschap verder geharmoniseerd door de invoering van diverse Europese richtlijnen en verordeningen. Daarnaast vindt het onderzoek in toenemende mate plaats in niet-academische opleidingsziekenhuizen (naast de universitair medische centra (UMC's), waar dit onderzoek traditioneel plaatsvond) en geschiedt het onderzoek steeds vaker in meerdere centra tegelijk. Deze dynamieken zorgen ervoor dat actoren zich aan dienen te passen door bijvoorbeeld het Nederlandse toezicht- en toetsingssysteem af te stemmen op de nieuwe vereisten van de Europese Unie (EU) of door een monitoringsysteem in ziekenhuizen te ontwikkelen. Om deze aanpassingen te

[26] In dit proefschrift verken ik de governance acties van actoren door het toepassen van institutionele theorieën als mijn analysemethoden. Ik hanteer hierbij de volgende brede definitie van governance: "het proces van het sturen van de samenleving en de economie ('hoe') door middel van collectieve actie en in overeenstemming met gemeenschappelijke doelen ('wat')" (Torfing et al., 2012, in Ansell & Torfing, 2022, p. 3). De Nederlandse vertaling van governance is besturen en is voor dit proefschrift in feite een te nauwe definitie. Een governance benadering is gebaseerd op het idee dat verschillende betrokken actoren toezien op de kwaliteit van medisch-wetenschappelijk onderzoek en dat in allerlei praktijken van toetsing en toezicht nader institutioneel werk verzet moet worden om deze kwaliteit te waarborgen. Deze benadering past bij het gekozen domein van medisch-wetenschappelijk onderzoek waarbij meerdere actoren betrokken zijn bij de toetsing en het toezicht. Om deze reden hanteer ik in deze samenvatting de Engels term governance.

identificeren, gebruik ik het concept 'institutioneel werk'; dit omvat activiteiten die actoren ondernemen om institutionele structuren te creëren, te onderhouden of te verstoren.

Empirisch beoogt deze studie te begrijpen hoe publieke en private actoren de ethische en wetenschappelijke kernwaarden interpreteren én vertalen naar acties ter bescherming van de deelnemers en borging van de wetenschappelijke integriteit. Deze actoren dragen steeds vaker een gedeelde verantwoordelijkheid voor het naar behoren functioneren van governance praktijken. De dataverzameling is voornamelijk gebaseerd op kwalitatieve onderzoeksmethoden en richt zich op het verzamelen van verhalen van betrokken actoren over hoe zij hun overtuigingen en praktijken interpreteren alsmede observaties van monitorings- en toezichtpraktijken.

Conceptueel levert deze studie een bijdrage aan academische en beleidsmatige debatten over het toekomstbestendig maken van beleid en praktijken rondom toezicht- en beoordelingssystemen. Door het belang van een governance-benadering – naast juridische en institutionele benaderingen – aan te tonen, wordt duidelijk hoe uitdagingen in medisch onderzoek kunnen worden aangepakt; zo'n geïntegreerde benadering is essentieel om ethische en wetenschappelijke waarden te beschermen en te waarborgen. Door het institutionele werk van onderling afhankelijke (toezichthoudende) actoren inzichtelijk te maken rondom drie met elkaar verbonden governance mechanismen– regels, ruimte en verantwoordelijkheden – wordt duidelijk op welke wijze actoren een zekere mate van veerkracht kunnen ontwikkelen. Deze veerkracht biedt hen de ruimte om flexibel om te gaan met veranderingen (dynamieken) terwijl ze tegelijkertijd voldoen aan regels en verantwoordelijkheden die essentieel zijn voor het beschermen en waarborgen van de kernwaarden of juist voor het afwegen van deze waarden tegen elkaar wanneer ze botsen.

Het medisch-wetenschappelijk onderzoek in Nederland kent een complex speelveld dat bestaat uit onder meer deelnemers, Medisch-Ethische Toetsingscommissies (METC's), de Centrale Commissie Mensgebonden Onderzoek (CCMO), sponsoren (ofwel de opdrachtgevers van of verantwoordelijken voor het onderzoek) en de Inspectie Gezondheidszorg en

Jeugd (IGJ). Dit speelveld wordt vooral gereguleerd door de Wet Medisch-wetenschappelijk onderzoek met mensen (WMO), die sinds 1999 van kracht is en bescherming biedt aan deelnemers die meedoen aan onderzoek. De regionale METC's zijn veelal verbonden aan één of meerdere ziekenhuizen. De CCMO treedt voor specifieke gevallen op als toetsingscommissie. De toetsingscommissies hebben de taak om de ethische en wetenschappelijke waarden van onderzoeksvoorstellen te beoordelen en te monitoren. De CCMO heeft in de WMO ook andere taken toebedeeld gekregen, zoals het opstellen van richtlijnen voor de toetsing van onderzoek en de erkenning en het toezicht houden op METC's. Sponsoren van medisch-wetenschappelijk onderzoek hebben een specifieke verantwoordelijkheid om de deelnemers te beschermen. Of het nu gaat om onderzoeken gefinancierd door de farmaceutische industrie of om door onderzoekers zelf geïnitieerde onderzoeken (zogeheten *investigator-initiated trials* of IIT's) in ziekenhuizen. De regelgeving vereist dat alle betrokken actoren zich aan dezelfde regels houden, ondanks hun mogelijke ongelijke situaties, bijvoorbeeld farmaceutische bedrijven beschikken over een breed scala aan experts en financiële middelen om de naleving van wettelijke vereisten te waarborgen, terwijl deze middelen minder beschikbaar zijn in het geval van IIT's. De Inspectie is verantwoordelijk voor het toezicht op lopend medisch-wetenschappelijk onderzoek.

De **onderzoeksvraag** richt zich op het begrijpen van het institutionele werk dat publieke en private actoren ondernemen om dynamische uitdagingen binnen de gelaagde governance structuur van medisch-wetenschappelijk onderzoek en publiek toezicht op te pakken. Het doel van de studie is om ons begrip te vergroten van het institutionele werk dat verschillende actoren verrichten om effectief in te spelen op de voortdurend veranderende uitdagingen binnen verschillende praktijken. Meer specifiek, deze studie analyseert de besturing op de volgende niveaus binnen het domein van medisch-wetenschappelijk onderzoek:

- de effecten van EU harmonisatie beleid op het publieke toezicht van klinische onderzoeken.
- de uitdagingen bij het publieke toezicht op lopende klinische onderzoeken.

- het waarborgen van datakwaliteit in door onderzoekers geïnitieerde onderzoeken in Nederlandse ziekenhuizen.
- de impact van onderzoekssamenwerking op de onderzoeksoutput in Nederlandse ziekenhuizen.

Elk van deze vragen is beantwoord in een empirisch hoofdstuk en is gepubliceerd als een wetenschappelijk artikel.

Hoofdstuk 2 richt zich op de impact van EU harmonisatiebeleid op het publieke toezicht van klinische onderzoeken. De EU-richtlijn *Clinical Trials Directive* (CTD) en de EU-verordening *Clinical Trials Regulation* streven ernaar om een goede klinische praktijk (*Good Clinical Practice*, GCP) van klinische onderzoeken in alle lidstaten te harmoniseren. Met Nederland als casestudy analyseert deze studie hoe pogingen om de CTD te implementeren een dynamisch proces van institutionele verandering en institutioneel werk in gang zetten. Dit proces leidde tot aanzienlijke verschillen tussen het beleid en de feitelijke praktijk. Daarom is het belangrijk om meer te weten te komen over de implementatie van harmonisatiebeleid.
Voor deze studie zijn verschillende belanghebbenden en Nederlandse en internationale toezichthouders geïnterviewd en inspectiebezoeken door de IGJ geobserveerd.

De studie toont aan dat Nederlandse wetgeving een nieuwe sturingslaag in een reeds gelaagd wetgevingskader creëerde. Dit kwam doordat de Nederlandse wetgever koos om zoveel mogelijk het bestaande Nederlandse systeem van toetsing en toezicht te behouden bij de implementatie van de CTD. In Nederland zijn de toetsingstaken niet ondergebracht bij één bevoegde instantie. Hierdoor diende de taken zoals voorgesteld in de CTD verdeeld te worden over de belangrijkste spelers in het publieke toezicht: de IGJ, de CCMO, de METC's, het ministerie van Volksgezondheid, Welzijn en Sport (VWS) en het College ter Beoordeling van Geneesmiddelen. Bovendien is, in tegenstelling tot de Europese regelgeving, de toetsing van ethische waarden en wetenschappelijke kwaliteit geïntegreerd in het Nederlands systeem.

In Nederland is gekozen om nieuwe regels toe te voegen aan bestaande regelgeving (in de institutionele theorie ook wel '*layering*' genoemd). Dit resulteerde in een complexe en gefragmenteerde organisatiestructuur in het

publieke toezicht, wat op zijn beurt weer leidde tot institutioneel werk door actoren, wat vervolgens verdere incrementele institutionele verandering teweegbracht. De nieuwe verdeling van verantwoordelijkheden leidde tot overlappende rollen in het toezicht op lopende onderzoeken, wat resulteerde in onduidelijkheid tussen de IGJ en METC's. Een aanvullende observatie is dat de IGJ beperkte toezichts- en handhavingsbevoegdheden heeft over entiteiten als farmaceutische bedrijven of *Contract Research Organisations* (CRO's) die in een internationale context opereren. Het is bijvoorbeeld onduidelijk of de sponsor of CRO van een internationale multicenter trial verplicht is om te reageren op de bevindingen van een nationale inspectie wanneer deze probeert te voldoen aan meerdere sets van regelgeving en verplicht is de interne protocollen consistent te houden.

Deze studie toont aan dat harmonisatieprocessen dynamische cycli kunnen creëren tussen institutionele verandering en institutioneel werk, wat leidt tot aanzienlijke verschillen in de manier waarop de EU-regels voor GCP worden vertaald naar de praktijken van de lidstaten. De implementatie van harmonisatiebeleid dient nauwgezet gevolgd te worden om te voorkomen dat onbedoelde gevolgen contraproductief zijn voor het doel van de harmonisatie: het waarborgen van zowel de bescherming van deelnemers als de betrouwbaarheid van de verkregen gegevens.

Hoofdstuk 3 onderzoekt hoe betrokken instanties bij het toezicht op lopende onderzoeken hebben gereageerd op externe uitdagingen van de afgelopen twee decennia, zoals harmonisatie van EU-regelgeving en incidenten. Daarnaast richt het zich op hoe deze instanties institutioneel werk verrichten om het Nederlandse regelgevingsregime te behouden, te herstellen of te verbeteren. In deze studie zijn internationale en nationale regelgevingsdocumenten geanalyseerd en interviews gehouden met verschillende actoren waaronder publieke toezichthoudende instanties en stafleden en raden van bestuur van ziekenhuizen.

In Nederland heeft EU-harmonisatie, gericht op het centraliseren en coördineren van het regelgevingsregime voor goede klinische proefpraktijken in lidstaten, paradoxaal genoeg geleid tot verdere fragmentatie. De dubbelzinnigheid en inefficiëntie bleven grotendeels onopgelost totdat een

ernstig incident in 2008 een katalysator voor verandering werd. Het incident betrof het Propatria onderzoek in een universitair ziekenhuis waarin de onderzochte behandeling leidde tot meer sterfgevallen onder patiënten die de behandeling kregen dan onder degenen die de placebo kregen. Dit incident leidde tot meerdere veranderingen in de institutionele vormgeving van de aansturing van medisch-wetenschappelijk onderzoek.

Ten eerste werd de verdeling van verantwoordelijkheden tussen de toezichthoudende instanties CCMO en IGJ verduidelijkt door het Ministerie van VWS. De IGJ en de CCMO werden gedwongen samen te werken tijdens het onderzoek naar de Propatria studie en dit leidde, in de loop van de tijd, tot een beter beheer van hun verantwoordelijkheden en een betere coördinatie van hun toezichthoudende taken. Ten tweede is de WMO in 2015 aangepast. Het melden van ernstige bijwerkingen (*serious adverse events*, SAE's) aan METC's werd verplicht gesteld voor alle onderzoeken die onder de WMO vallen om de veiligheid van de deelnemers te waarborgen. METC's hadden echter te maken met financiële beperkingen, waardoor het tijdig beoordelen van protocollen hun primaire focus bleef en dit verminderde hun vermogen om zich aan te passen aan de externe uitdagingen. Ten derde heeft het Ministerie van VWS de CCMO een nieuwe verantwoordelijkheid gegeven: de jaarlijkse rapportage over het aantal SAE's en de gevolgen voor de veiligheid van deelnemers. De CCMO heeft in reactie hierop een digitale tool ontwikkeld om de SAE-rapportages te vergemakkelijken. Ten vierde heeft het Propatria incident ertoe geleid dat de IGJ de Raden van Bestuur van ziekenhuizen is gaan aanspreken op hun rol als sponsors van door onderzoekers geïnitieerde onderzoeken (IIT's). Dit verduidelijkte tevens hun bijbehorende toezichthoudende verantwoordelijkheden op het lopende onderzoek dat binnen hun instellingen plaatsvindt zoals beschreven in de WMO. De IGJ wees Raden van Bestuur op een terugkerende bevinding in deze inspecties: de noodzaak om een uitgebreid kwaliteitssysteem op te zetten dat auditing- en monitoringprocessen omvat. Daarnaast werd de betrokkenheid van een actor buiten het regelgevende kader - de vereniging Samenwerkende Topklinische Ziekenhuizen (STZ) - van belang om het toezicht op lopende onderzoeken te versterken. De STZ ontwikkelde standaardwerkprocedures

ter aanvulling van kwaliteitsborgingshandleidingen voor de aangesloten opleidingsziekenhuizen en faciliteerde de uitwisseling van geleerde lessen en '*best practices*'.

Deze studie concludeert dat het publieke toezicht op lopende onderzoeken in Nederland gefragmenteerd is omdat de verantwoordelijkheden en middelen ongelijk verdeeld zijn tussen de betrokken actoren. In landen met toetsings- en toezichtsystemen die, zoals het systeem in Nederland, verschilt van de EU, dienen publieke toezichthoudende instanties veel institutioneel werk te verrichten om zich aan te passen aan nieuwe EU-regelgeving. Dit terwijl ze hun traditionele regelgevende mechanismen, die de veiligheid van mensen waarborgen, blijven beschermen. Nationale regelgevende tradities bieden echter ook nieuwe kansen om kwaliteitsborging van klinische onderzoeken te verbeteren.

Hoofdstuk 4 onderzoekt de complexiteit van regelgeving met betrekking tot door onderzoekers geïnitieerde onderzoeken (IIT's). Deze complexiteit betekent een grote last voor ziekenhuizen op het gebied van naleving, documentatie en trainen van onderzoekers. Veel ziekenhuizen proberen daarom de regeldruk te verlichten door een alternatief kwaliteitsmanagementsysteem (*quality management system*, QMS) in te voeren. Om te onderzoeken hoe het QMS voor IIT's in Nederlandse ziekenhuizen is georganiseerd, hebben we de theoretische concepten van 'mentoring' en 'monitoring' toegepast.

In de klinische praktijk en internationale richtlijnen wordt monitoring gezien als de standaard benadering van kwaliteitsborging voor lopende onderzoeken. Ziekenhuizen hebben echter monitoringprogramma's geïmplementeerd die lijken op mentoring. Het contrast tussen deze beide typen is in de praktijk minder uitgesproken, omdat beide elementen van naleving en feedback voor leren in de praktijk combineren. Zowel monitoren als mentoren spelen een faciliterende rol bij het bevorderen van verantwoord onderzoeksgedrag en het interpreteren van regelgeving. Echter, in een monitoringomgeving is leren eenrichtingsverkeer, van monitor naar onderzoeker; terwijl mentoring zich richt op wederzijdse ondersteuning en leren, waarbij de mentor en onderzoeker vaak flexibel van rol wisselen.

Daarnaast is een ander verschil dat waar monitoring zich richt op een centraal geleid programma voor de beoordeling van onderzoekspraktijken, dit bij mentoring decentraal en horizontaal is. Monitoring leidt daarbij tot het opstellen van regels waar onderzoekers zich aan moeten houden terwijl mentoring zich meer richt op het geven van peer feedback. Voor ziekenhuizen is mentoring aantrekkelijk omdat het gesprekken tussen onderzoekers op gang brengt over de afweging tussen de ethische en methodologische vereisten van onderzoek en daarmee helpt de relevante normen te internaliseren.

Om problemen in elk systeem aan te pakken, zijn de autoriteit van de Raad van Bestuur en hun relatie met stafleden cruciaal. Raden van Bestuur omarmen steeds meer hun verantwoordelijkheid voor het QMS in IIT's. Het onderzoek naar het Propatria-incident en daaropvolgende inspectiebezoeken benadrukten de noodzaak van verbeterd kwaliteitsmanagement om de veiligheid van deelnemers en methodologische kwaliteit tijdens onderzoeken te waarborgen. Deze ontwikkelingen, samen met de faciliterende ondersteuning van de STZ, openden mogelijkheden om te experimenteren met nieuwe mentoringpraktijken. Ziekenhuizen boden mentoren, monitoren en onderzoekers een omgeving en setting die bevorderlijk was voor leren. Dit omvatte het bieden van praktische ondersteuning aan GCP-gekwalificeerde onderzoekers bij het afstemmen van hun onderzoeksprocedures op de wettelijke vereisten. Hierdoor werden zowel monitoring als mentoring integrale componenten van QMS's binnen opleidingsziekenhuizen en UMC's. De Raden van Bestuur hadden de verantwoordelijkheid voor de implementatie van deze systemen gedelegeerd aan stafafdelingen. De stafafdelingen werden dus verantwoordelijk en aansprakelijk voor kwaliteitscontrole, verbetering en waarborging van IIT's, terwijl de Raden van Bestuur, als sponsor, de algehele verantwoordelijkheid behielden.

Hoofdstuk 5 gaat dieper in op de dynamieken van samenwerking op het gebied van onderzoek. In Nederland zijn UMC's primair verantwoordelijk voor het uitvoeren van medisch onderzoek en het leveren van zeer gespecialiseerde zorg. Het TopZorg-programma was een beleidsexperiment waarin drie niet-academische opleidingsziekenhuizen financiering ontvingen van het ministerie van VWS om ook medisch onderzoek uit te voeren en zeer

gespecialiseerde zorg te leveren in specifieke domeinen. Deze studie onderzoekt de resultaten van onderzoekssamenwerking voor alle Nederlandse UMC's en opleidingsziekenhuizen en specifiek de vier domeinen van twee niet-academische opleidingsziekenhuizen die deelnamen aan het TopZorg-programma. Daarnaast belicht deze studie het organisatorische grenzenwerk dat deze TopZorg ziekenhuizen verrichtten om productieve onderzoekssamenwerkingen te bevorderen. Hier beschouwen we grenswerk als een specifiek type institutioneel werk dat inspanningen omvat om grenzen tussen organisaties of domeinen te creëren, te onderhouden of te ondermijnen. Voor deze studie werd een gemengde kwantitatieve en kwalitatieve benadering gebruikt.

De kwantitatieve analyse laat zien dat, gedurende de studieperiode, de internationale samenwerking tussen alle ziekenhuizen toenam, terwijl nationale samenwerking en onderzoeken uitgevoerd door één ziekenhuis licht daalden. De samenwerkingsinspanningen correleerden met hogere impactscores, en internationale samenwerking scoorde hoger dan nationale samenwerking. Zestig procent van alle publicaties van niet-academische opleidingsziekenhuizen werd geproduceerd in samenwerking met UMC's, terwijl bijna 30% van de publicaties van de UMC's het resultaat was van dergelijke samenwerking. Niet-academische opleidingsziekenhuizen lieten een hogere mate van samenwerking zien met het geografisch dichtstbijzijnde UMC, terwijl TopZorg ziekenhuizen binnen hun specialistische domeinen prioriteit gaven aan expertise boven geografische nabijheid.

Het grenzenwerk van de TopZorg ziekenhuizen omvat het afstemmen van onderzoeksactiviteiten op de organisatorische identiteit, het versterken van de onderzoeksinfrastructuur en het vinden en mobiliseren van strategische partnerschappen met academische partners. Deze inspanningen waren gericht op het vergroten van de geloofwaardigheid en aantrekkelijkheid van het ziekenhuis als samenwerkingspartners. Bovendien onthult dit grenswerk een dubbele dynamiek, doordat het grenzen opende en beschermde. Enerzijds verstevigden de betrokken ziekenhuizen hun samenwerkingspositie en verbeterden of versterkten ze de wetenschappelijke waarde in onderzoekssamenwerkingen met de academische wereld. Anderzijds bereikten ze niet het onderliggende doel van het kortlopende TopZorg

programma: het opzetten van structurele financiering voor zeer gespecialiseerde zorg en medisch onderzoek in niet-academische opleidingsziekenhuizen.

Kortom, onderzoekssamenwerking tussen niet-academische opleidingsziekenhuizen en UMC's, met name als dit ook internationale samenwerking betreft, is lonend in termen van publicaties en impact. De Topzorg ziekenhuizen gebruikten de middelen van het programma om grenzenwerk uit te voeren dat gericht was op het worden van een aantrekkelijke en geloofwaardige samenwerkingspartner voor de academische wereld. Lokale factoren als onderzoeksgeschiedenis, strategische domeinfocus, interne expertise, patiëntenstromen, infrastructuur en netwerkrelaties beïnvloedden de samenwerkingsdynamiek binnen TopZorg-ziekenhuizen en tussen hen en UMC's.

Hoofdstuk 6 belicht de belangrijkste thema's uit dit onderzoek. Het landschap van medisch-wetenschappelijk onderzoek wordt voortdurend gevormd door een veelheid aan dynamische ontwikkelingen, zowel extern als intern. Deze dynamieken resoneren op alle governance niveaus binnen medisch-wetenschappelijk onderzoek. Als er nieuwe uitdagingen ontstaan, voelen de actoren een dringende behoefte aan herijking en reparatiewerkzaamheden en zoeken zij voortdurend naar pragmatische oplossingen om ethische en wetenschappelijke kernwaarden te activeren, te articuleren en te waarborgen. De intenties die ten grondslag liggen aan verschillende regelgevingen, geworteld in kernwaarden, kunnen dus zo dienen als moreel kompas voor actoren in dit veld.

Op het gebied van governance van medisch-wetenschappelijk onderzoek is het van belang dat de relevante actoren samenwerken. Dit is zeker het geval in de Nederlandse context, waar meerdere actoren ook betrokken zijn bij de toetsing en het toezicht. Het vergt constant werk van de actoren om die afstemming te bereiken. Dit proefschrift laat bovendien zien dat hoewel dit redelijk werkt bij het vooraf beoordelen van onderzoeksvoorstellen, het monitoren van een onderzoek gedurende de uitvoering nog uitdagingen oplevert.

Bovendien is het governance systeem van medisch-wetenschappelijk onderzoek onderhevig geweest aan een complex en gefragmenteerd regelgevingskader als gevolg van historische ontwikkelingen, zoals de talrijke lokale METC's die in de periferie opereren. Dergelijke fragmentatie heeft geleid tot afhankelijkheden van de middelen en de acties van en interacties met andere niveaus, wat van invloed is op de verwezenlijking van systeemdoelen en -taken. Dit heeft nauwe coördinatie, afstemming en samenwerking tussen actoren op alle niveaus in Nederland noodzakelijker gemaakt dan elders in de EU.

Institutioneel werk is een essentieel onderdeel van verschillende governance praktijken om dynamische ontwikkelingen effectief aan te pakken. Deze studie toont aan dat het institutionele werk van actoren draait om drie onderling verbonden governance mechanismen: regels, ruimte en verantwoordelijkheden, gericht op het beschermen van ethische en wetenschappelijke kernwaarden. Regels omvat wetten, richtlijnen, verordeningen en standaarden die moeten worden nageleefd. Ruimte verwijst naar de flexibiliteit en autonomie die actoren nodig hebben om kernwaarden in specifieke praktijken binnen die regels te interpreteren en te beschermen. Verantwoordelijkheden omvat het toewijzen van taken en plichten aan verschillende actoren, wat kan leiden tot een hoge mate van onderlinge afhankelijkheid bij de uitvoering van taken in medisch wetenschappelijk onderzoek. Door alle drie de governance mechanismen coherent te gebruiken, kunnen actoren een veerkrachtig governance kader opzetten dat in staat is om uitdagingen aan te pakken en de wetenschappelijke integriteit en ethiek van medisch-wetenschappelijk onderzoek te beschermen.

'Veerkracht' wordt gedefinieerd als het vermogen om zich voor te bereiden op, te reageren op of te herstellen van onvoorziene problemen of verstoringen, terwijl de kernwaarden gewaarborgd blijven. In het streven naar veerkracht dienen actoren in het toezicht- en toetsingssysteem effectief samen te werken en institutioneel werk te verrichten om zo een optimale balans tussen regels, ruimte en verantwoordelijkheden te bevorderen. Dit houdt in dat actoren zowel structuur als flexibiliteit krijgen bij het reageren op dynamische uitdagingen. Het bereiken van deze balans optimaliseert de

actualisering van de kernwaarden. Omgekeerd kan een onevenwichtigheid tussen regels, ruimte en verantwoordelijkheden de bescherming van deze waarden in gevaar brengen of belemmeren. Dit 4R-model (*rules, room, responsibility, resilience*) kan instrumenteel zijn bij het diagnosticeren of de verschillende governance mechanismen in evenwicht zijn tussen onderling afhankelijke actoren.

Momenteel is de werking van de WMO opnieuw verder ingeperkt door de invoering van de *Clinical Trials Regulation* van de Europese Unie. Bepaalde bepalingen van de WMO zijn niet van toepassing verklaard met een directe verwijzing naar EU-wetgeving. De EU speelt nu en zal naar verwachting een substantiële rol blijven spelen bij het reguleren van medisch-wetenschappelijk onderzoek met mensen, als onderdeel van haar inspanningen om regelgeving te harmoniseren. In het licht van deze inspanningen is het van groot belang om te overwegen hoe het Nederlandse toezicht- en toetsingssysteem het beste toekomstbestendig kan worden gemaakt. Daarbij is het van belang om de relatie tussen de vier R's in de gaten te houden, met name omdat EU-regelgeving neigt naar het beklemtonen van regels boven ruimte.

De vierde wetsevaluatie van de WMO, waarvan ik mede coauteur ben, schetst verschillende aanbevelingen om het Nederlandse systeem toekomstbestendig te maken. Deze wetsevaluatie stelt oplossingen voor voor het probleem van de dubbele rol van de CCMO, namelijk enerzijds het toezicht op METC-activiteiten en anderzijds het standaardiseren van deze activiteiten via richtlijnen en het ondersteunen van de METC's. Eén oplossingsrichting is het herstructureren van de verantwoordelijkheden van de CCMO door haar toezichthoudende functie te beëindigen en deze verantwoordelijkheid over te dragen aan de IGJ. Dit zou de coördinerende rol van de CCMO versterken en haar de nodige institutionele ruimte bieden om samenwerking binnen het toetsingssysteem te bevorderen en te organiseren.

De wetsevaluatie richt zich ook op de uitdagingen die EU-regelgeving en harmonisatie vormen voor onderzoekers die IIT's uitvoeren. Dergelijke studies worden geconfronteerd met aanzienlijke uitdagingen, omdat ze vergeleken met farmaceutische bedrijven, beperkte middelen en

ondersteuning tot hun beschikking hebben. Ondanks deze uitdagingen (strenge regels en gedefinieerde verantwoordelijkheden) zijn IIT's vaak van belang voor de samenleving, omdat ze worden aangestuurd door klinische noodzakelijkheden in plaats van commerciële belangen. Complexe en gedetailleerde vereisten, zoals die worden opgelegd door EU-regelgeving, kunnen echter ook als belemmeringen werken en van invloed zijn op het type onderzoek dat wordt uitgevoerd. Belangrijke onderwerpen voor wetsevaluatie zijn onder meer het formuleren van een visie met betrekking tot IIT's door entiteiten zoals de STZ, de NFU en ziekenhuizen, het identificeren van de ondersteuningsvereisten voor onderzoekers en het faciliteren van IIT's binnen ziekenhuisomgevingen. Met andere woorden, institutionele regelingen die de levensvatbaarheid van IIT's bevorderen, verdienen volledige aandacht in de komende evaluaties.

Concluderend, effectief reageren op veranderende omstandigheden in medisch-wetenschappelijk onderzoek vereist de integratie van drie governance mechanismen, namelijk regels, ruimte en verantwoordelijkheden. Deze mechanismen zorgen er gezamenlijk voor dat actoren binnen elke governance praktijk leren, improviseren en zich aanpassen, terwijl ze de ethische en wetenschappelijke kernwaarden hooghouden. Het behouden van de integriteit en betrouwbaarheid van wetenschappelijke inspanningen te midden van dynamische uitdagingen en kansen vereist het in evenwicht brengen van wetenschappelijke doelen met ethische kernwaarden, zoals het minimaliseren van risico's voor deelnemers en het verzekeren van geïnformeerde toestemming. De synergie van regels, ruimte en verantwoordelijkheden stelt actoren in staat om door de complexiteiten te navigeren die inherent zijn aan medisch-wetenschappelijk onderzoek en waarborgt de veerkracht die nodig is om ethische en wetenschappelijke kernwaarden te bevorderen.

Dankwoord

Het werken aan dit promotieonderzoek is een proces van zelfontplooiing geweest. Het past bij een leven lang leren. Met gedrevenheid omdat een eerdere poging strandde. Ik wilde graag aan mijzelf bewijzen dat ik zo'n proces kon volbrengen. Het promotietraject geeft mij een yin-yang gevoel. Dit betekent voor mij plezier hebben en jezelf uitdagen. Hierbij is jezelf uitdagen een positieve formulering van iets doen dat buiten je comfortzone ligt. Deze twee waarden, plezier hebben en jezelf uitdagen, kunnen wat mij betreft niet afzonderlijk van elkaar bestaan en zorgen zowel voor harmonie als veerkracht.

Waar ik van genoot was het persoonlijke contact met de respondenten. In deze gesprekken deelden zij hun passie, toewijding en ook de uitdagingen die zij ervaarden in hun werk en in de samenwerking met andere partijen. Ik heb getracht hen zo goed en zorgvuldig mogelijk te informeren over de verworven inzichten. Ik wil oprecht alle respondenten bedanken voor hun vertrouwen, openheid en de tijd die zij wilden vrijmaken.

En dan begon de zoektocht …

- naar het aanbrengen van samenhang in de verzamelde gegevens met diverse theorieën. Het werd interessant als er tegendraadse inzichten waren opgehaald die haaks stonden op meer gebruikelijke interpretaties.
- naar het goed verwoorden van ruwe gedachtenspinsels om vervolgens stapsgewijs te komen tot een gestructureerde verhaallijn.
- naar het vinden van tijd, rust en aandacht om aan het onderzoek te werken naast het werk en het gezin. Menig verdiepend inzicht werd in nachtelijk uren gevonden.

Al deze zoektochten hebben mij verrijkt als mens. Het geeft voldoening dat het einde in zicht is.

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De blauwe streep : oprichting van de Centrale Commissie Mensgebonden Onderzoek (hoofdstuk 2 en 3)

Het linker deel illustreert het publieke toezicht van klinisch onderzoek

De gele stip: het Propatria incident (hoofdstuk 3)

De twee gele lijnen: monitoring en mentoring (hoofdstuk 4)

Het rechter deel staat voor het onderzoek dat wordt uitgevoerd in ziekenhuizen

Het raster: de verschillende samenwerkende ziekenhuizen als de domeinen van de TopZorg opleidingsziekenhuizen (hoofdstuk 5)

Mijn lieve ouders, Henk en Coby (of liever gezegd Coco), jullie steun gedurende dit traject was echt bijzonder. Fijn dat jullie altijd voor mij klaar stonden en bereid waren mij te ondersteuning met de verzorging van C-J. De zorgzaamheid en het doorzettingsvermogen heb ik van mijn lieve moeder geërfd.

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Portfolio

Workshops and training

2019 Qualitative coding with ATLAS.ti (EUR/Rotterdam)
2018 Training Speak up dear! NobbeMieras (EUR/Rotterdam)
2016 Academic Writing for PhD students instituut Beleid & Management Gezondheidszorg (EUR/Rotterdam)
2014 Integrity game / dilemma game / oath signing

Peer-reviewed publications (this thesis)

Van Oijen, J. C. F., Van Dongen-Leunis, A., Postma, J., Van Leeuwen, T., & Bal, R. (2024). Achieving research impact in medical research through collaboration across organizational boundaries. Insights from a mixed methods study in the Netherlands. *Health Research Policy and Systems, 22,* 72. https://doi.org/10.1186/s12961-024-01157-z

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Çelik, S., Veentra, M., Van Oijen, J., & Sabajo, N. (2022). *Daarom stappen ze op. Vertrekmotieven van aspiranten en jong-afgestudeerden bij de politie*. Lectoraat Diversiteit & Inclusie, Hogeschool Leiden.

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Çelik, S. (red.), Geutjes, L.-L., Van Oijen, J., Sabajo, N., & Van Miert, V. (2021). *Een kritische blik in de spiegel. Lessen en bouwstenen voor een inclusieve hogeschool*. Lectoraat Diversiteit, Hogeschool Leiden.

Grit, K. J., & Van Oijen, J. C. F. (2015). *Toezicht op het medisch-wetenschappelijk onderzoek met mensen: Het in kaart brengen van een multi-centered speelveld*. Instituut Beleid & Management Gezondheidszorg, Erasmus Universiteit Rotterdam.

Presentations

Conferences

2021 Netherlands Institute of Governance conference, online due to the COVID-19 pandemic, panel: Spanning boundaries in collaborative governance. Title abstract and manuscript: *Achieving research impact in medical research through collaboration across organizational boundaries. Insights and lessons from a national survey and policy experiment in the Netherlands.*

2020 International Research Society for Public Management (Finland, Tampere University), panel: Healthcare management and health policy. The abstract was approved. The conference was cancelled due to the COVID-19 pandemic. Title abstract: *Assuring data quality in investigator initiated trials in Dutch hospitals: balancing between monitoring and mentoring.*

2018 European Consortium for Political Research (Hamburg), panel: United in diversity? Implementation and performance in multi-level governance I. Title abstract and manuscript: *The effects of EU harmonization on national public supervision of ongoing trials.*

2018 WHO Collaborating Centre for Pharmaceutical Policy and Regulation (Utrecht), panel: Clinical trials. Title abstract and manuscript: *The effects of EU harmonization on national public supervision of ongoing trials.*

2015 VIDE jaarcongres 'Toezicht ontmoet wetenschap', poster presentation '*Toezicht op Medisch Wetenschappelijk Onderzoek met mensen*.

In the field

- Meeting 'Raad Wetenschap STZ' 16 October 2016.
- STZ meeting science coordinators 15 March 2016.

Other activities

2020-present Member of the Central Ethics Research Committee Hogeschool Leiden.

2014-present Advisor to the Supervisory Board of the Merel Foundation, a daycare centre for young children with autism, and a member of the Supervisory Board until 2023.

About the author

Jacqueline van Oijen (1966) completed the HEAO programme (Higher Education in Economics and Administrative Studies) and then went on to pursue her Masters' degree (*doctorandus*) in Health Policy & Management at Erasmus University in Rotterdam, specializing in quality management. Jacqueline led projects at TNO Prevention & Health (1995-1999) focused on quality improvement in higher education and healthcare. Her work concentrated on developing quality assurance standards for hospitals and supporting hospital accreditation processes.

At Leiden University of Applied Sciences, she has had various roles, including quality coordinator for the Faculty of Management & Business and coordinator of the Advanced Post-Bachelor's Management Programme. Since 2010, she has taught in the Healthcare Management bachelor's programme, where she leads modules in research and leadership. Additionally, since 2005, she has been involved with various research groups within the Faculty of Management & Business and is currently engaged with the Knowledge Centre for Applied Broad Prosperity.

She began her PhD in 2014 at the Erasmus School of Health Policy & Management, focusing on the public supervision of medical research under the Medical Research Involving Human Subjects Act (WMO) as part of the 'Academische Werkplaats Toezicht' programme. This project inspired her to explore how data quality is ensured in investigator-initiated trials at university medical centres (UMCs) and teaching hospitals. In 2019, she had the opportunity to work with data from the TopCare programme—a four-year policy experiment—utilizing bibliometric analysis and interview data collected throughout the programme. Additionally, in collaboration with the Centre for Science and Technology Studies, she was involved in a decade-long analysis of publication trends across Dutch university medical centres and teaching hospitals. In 2023, as part of the WMO's fourth legislative evaluation, she assessed the functioning of Dutch Medical Research Ethics Committees.

The landscape of medical research is complex and constantly evolving. This complexity becomes especially evident when actors need to balance the ethical and scientific values that protect research participants with considerations of scientific integrity. These two key values, established in international treaties, form the bedrock of all laws, regulations and standards governing medical research and its supervision. While these values are beyond dispute, ensuring them in a complex and dynamic environment remains a challenging task for actors.

This study explores the work done by public and private actors to respond to such dynamics – for example EU harmonization policies, the shifting of research activities to non-academic teaching hospitals, and the complexities of multicentre trials – while continuing to uphold these key values. These actors adapt to change in order to maintain, restore and improve Dutch regulatory structures. They seek practical solutions, experiment, reflect and learn, while also finding room to interpret rules and share responsibilities through coordination and alignment work. By making coherent use of three governance mechanisms – rules, room and responsibilities – actors can establish a resilient governance framework that addresses challenges and safeguards the ethics and integrity of medical research, both now and in the future.