Effects of EU harmonization policies on national public supervision of clinical trials: A dynamic cycle of institutional change and institutional work

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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 EU Clinical Trials Directive 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 EU Clinical Trials Directive 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.

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1. 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 [1] to be enacted in 2018 will replace the EU Clinical Trials Directive 2001/20/EC (EUCTD) [2]. 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 EU Clinical Trials Directive to harmonize the international regulatory framework for clinical trials has not been fully achieved [3–7]. The new Regulation aims to create an environment that is favourable for conducting clinical trials for all EU Member States [8]. It provides measures to cut red tape, simplify the rules, and ensure that rules for conducting clinical trials are consistent throughout the EU [9].

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 determines how institutional 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 [10] and the concept of institutional work [11].

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.

2. 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 [10]. By following Streeck and Thelen [12], 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 [10]. Additionally, actors with different interests and perspectives can operate strategically in their institutional environment, which can instigate further incremental institutional change [10,12–14].

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 [15]. 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 [11,16]. 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. 17]; however, there are also case studies of complex policy change processes that show the dynamic interaction between different types of change [e.g. 18–22]. 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.

3. 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 Health-care 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.

4. 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 (4.1). 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 (4.2) and conversion in the international practice of multicenter trials (4.3). In the discussion and conclusion, we reflect on the consequences of these findings for the upcoming Regulation.

4.1. 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 labeled 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 [23]. Next, the Declaration of Helsinki was established for medical doctors conducting biomedical research [24]. It formed the basis for the ethical principles that underlie the good clinical practice (GCP) guidelines [25] that followed (see Fig. 1). In an effort to overcome GCP inconsistencies between countries, the International Council on 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 [26]. 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 [27]. 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) [28] 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 [3,29], but the laws regarding the supervision of clinical trials varied significantly between them. In an endeavor for harmonization, the EU enacted the first Clinical Trials Directive (2001/20/EC) [2] 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 EUCDT 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 regulations. Other countries, such as France, Finland, Ireland, and the Netherlands, integrated the EUCDT into existing law. In the Netherlands, a new article on clinical trials was added to the WMO (2006) [29, Articles 13a–13r].

In order to provide greater protection to its subjects, the EUCDT 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 [2, 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 [29]. 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 Com-

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**Fig. 1.** Overview distinguishing the multilevel legislative framework concerning clinical trials in the Netherlands (1964–2016).
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<td><strong>Decentralized accredited medical research ethics committees (MRECs)</strong></td>
<td>“The research protocol must have been approved by a MREC which is competent to give such approval . . .” (Article 2)</td>
<td>Member States: Ethics committee</td>
<td>“The sponsor of a clinical trial may not start until the ethics committee has issued a favorable opinion . . .” (Article 9)</td>
<td>MREC</td>
<td>“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) 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 MREC is the reviewing committee. (Article 13i)</td>
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<td><strong>Central Committee on Research Involving Human Subjects (CCMO)</strong></td>
<td>“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)</td>
<td>Competent authority</td>
<td>“. . .the competent authority of the Member State concerned has not informed the sponsor of any grounds for non-acceptance.” (Article 9)</td>
<td>Competent authorities: (1) Ministry of Health, Welfare and Sport, (2) CCMO</td>
<td>“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)</td>
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<td>• Checks whether a MREC meets obligations (accreditation) (Article 16)</td>
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<td>• “Inspection”: the act by a competent authority of conducting an official review of documents, facilities, records, quality assurance arrangements . . .” (Article 2)</td>
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<td>• Oversees the operations of MRECs and can set up new directives regarding their operations (Article 24)</td>
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<td>• Act as reviewing committee for specific fields of research (Article 19)</td>
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<td><strong>Dutch Health Care Inspectorate</strong></td>
<td>“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)</td>
<td>Competent authority: (3) Dutch Health Care Inspectorate</td>
<td>“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)</td>
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<td>• The Inspectorate is also responsible for conducting inspections, but does not assess research protocols.</td>
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<td><strong>Medicines Evaluation Board (MEB)</strong></td>
<td>The MEB assesses and monitors the efficacy, risks, and quality of human medicinal products. (<a href="http://english.cbg-meb.nl/about-meb">http://english.cbg-meb.nl/about-meb</a>)</td>
<td>Competent authority: (4) MEB</td>
<td>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)</td>
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mittee 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)

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 [10,12,30,31]. 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.

4.2. : 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 [29,Article 13],4 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 [32]. 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 [29,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-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 [33] and 2012 [34].

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.

4.3. : 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 [2,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 [35]. However, it is challenging to reach a consensus between members of the EMA on the most accu-
rate 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.

5. 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 [3–7]. 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. 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.

6. 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 ineffective 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” [37]. 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.

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