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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 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.

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 EUCTD 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

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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 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.

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