Research Policy xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Research Policy

journal homepage: www.elsevier.com/locate/respol

Testing regimes in clinical trials: Evidence from four polio vaccine trajectories

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ARTICLE INFO

Article history:
Received 10 March 2015
Received in revised form 21 January 2016
Accepted 6 December 2016
Available online xxx

Keywords:
Clinical trial
Vaccine
Medical innovation
Research translation
Research governance

ABSTRACT

This paper highlights distinctive features of a neglected class of economic activity in the domain of medical innovation, namely the creation of testing regimes in clinical trials, asking how their nature might be expected to affect innovation of medical technology. It argues firstly that clinical trials are not simply about passively validating an already well-known technology and verifying its safety. Rather, clinical trials are part of a more active process of learning that allows pharmaceutical innovations to be useful outside the laboratory. It argues secondly that product development can proceed along a number of long and costly paths before a product's behaviour in actual practice becomes clear, which can make selecting between alternative courses of action difficult. Thus, product choice and product development need to go hand-in-hand. To consider these arguments, the paper maps out four trajectories of polio vaccine development, tracing their paths through clinical trials since the 1950s, and describes some of the defining features of testing regimes for medical innovation. These include institutions that integrate knowledge and co-ordinate skills in testing processes, and capabilities for allocating testing resources, managing testability constraints, sharing knowledge and improving commensurability between testing communities.

1. Vaccine innovation and research translation: what are the needed institutions?

Epidemics periodically emerge as policy priorities, prompting calls for new vaccines (for example avian influenza, HIV, Ebola). Policy discussion often focuses on how firms can be given exemptions from regulatory barriers so that candidates can be rushed through clinical trials and certified for the market, especially when framed as international emergencies. This assumes a rather limited role for the range of institutions engaged in medical innovation outside of the laboratory, wherein clinical trials might even be seen as a mere regulatory hurdle that is imposed on firms before certifying products as being safe for the market. Vaccine innovation is often characterised as a process where research is not only translated into a product, but it is one that can be accelerated if only the social validation and bureaucracy of clinical trials can be streamlined.

The purpose of this paper is to draw attention to a neglected area of innovation study, namely the creation of testing regimes in clinical trials, asking how their nature might be expected to affect innovation of vaccines and perhaps also other medical technologies such as pharmaceutical drugs and devices. The paper describes some of the defining features of testing regimes by drawing together ideas from studies of innovation, evolutionary economics, and sociology of science and technology. Pharmaceuticals are becoming increasingly difficult to develop (Hopkins et al., 2007; Scannell et al., 2012; Gittelman, 2016). They exhibit high levels of attrition and few candidates make it to the costlier clinical phases (Arrowsmith, 2013). The few that do make it to clinical trials are seen as candidates that await confirmation of whether or not they are safe and effective. This understates the extent to which many of these candidates are unfinished products when they reach clinical trials and undergo considerable further development in a testing regime in order to *become* safe and effective. This paper shows that testing regimes are expensive to set up and maintain, and entail the creation of both physical and non-physical 'knowledge' infrastructure.

The paper makes two claims. First, clinical trials (i.e. testing that takes place in humans) are not simply about passively validating an already well-known technology and verifying its safety. Rather, clinical trials are part of a more active process of learning that allows pharmaceutical innovations to be useful outside the laboratory. Vaccines provide an extreme context to test this claim. Unlike most other medical technology vaccines are usually intended for people who are already healthy, which heightens

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http://dx.doi.org/10.1016/j.respol.2016.12.001
0048-7333/

concern for safety. There is special concern for product development to take place well in advance of clinical phases. Yet, even in vaccine innovation where safety is the paramount regulatory and social concern – to many it is the only concern (see Yaqub et al., 2014) – we shall see that the search for efficacy extends well into the clinical phases and how, over the course of the vaccine's 'career' (Blume 1992; Hopkins, 2006), the learning process becomes more governance intensive in the clinical phases (for a direct comparison to learning in pre-clinical stages, see Yaqub and Nightingale, 2012). If science does not lead to a clear and costless path to technology then, even in a case like vaccines, there is a need to understand what else is needed for product development, and what activities are going on under the banner of clinical trials and regulation.

Second, within a vaccine's career, multiple trajectories can be pursued (Dosi, 1982; von Tunzelmann et al., 2008; Rip, 2012). Although possible trajectories may become apparent by learning in laboratories and animals, the overall performance characteristics of the different trajectories operating in different systems will not have been revealed in their entirety. Product development can proceed along a number of long and costly paths before a product's behaviour in actual practice becomes clear, which can make selecting between alternative courses of action difficult.[1] Thus, product choice and product development need to go hand-in-hand.

The paper will substantiate these two claims through historical case study. Below, I develop a framework for analysing the case study by defining salient features of testing regimes. The paper contributes directly to a stream of literature concerning the evolution of medical knowledge (Gelijns and Rosenberg, 1994; Mina et al., 2007; Rosenberg, 2009; Nelson et al., 2011; Consoli et al., 2016). It also draws on history of technology and engineering studies literature concerning the accumulation of technological knowledge (Layton, 1974; Constant, 1980; Vincenti, 1990, Rosenberg and Steinmueller, 2013), and specific work indicating that the rate and direction of vaccine innovation is influenced by the ability to set up 'testing regimes' and test repeatedly (Nelson, 2008; Yaqub, 2010; Yaqub and Nightingale, 2012). The intuition here is that all complex technologies share a protracted process of development, be they vaccines or turbojets.[2]

2. Testability, trajectories and infrastructure: a framework for analysis

Technologists test ideas with instruments and skill under varying conditions, according to shared standards, and with the active participation of co-ordinating institutions. I refer to this triad of elements (conditions, instruments, and institutions) as a testing regime. We will see in the empirical section how the resulting *testability* of trajectories can differ with significant social consequences (in terms of the characteristics of the vaccines we end up with and the infrastructure organised around them).

Testing regimes do not proceed aimlessly, they require a 'social vision' set out by technical and practitioner communities as well as broader communities (Blume 1992:64-70). This is because technologies have a purpose that is not completely inherent to their physical properties (Polanyi, 1958:328). Purpose and function combine to form ideas for operational principles (how a technology works) (Vincenti, 1990:209), and social visions are formed around which operational principles can accelerate and develop as a trajectory within a vaccine's career, often in plurality because theory is a weak guide to practice (Blume 1992; Yaqub, 2010).[3]

Testing of operational principles proceeds through experimental stepping-stones, by building up understanding in simplified animal models before more realistic testing is undertaken in humans (Yaqub and Nightingale, 2012). Testing conditions are therefore controlled to trade-off ease of learning (simplicity) against clinical relevance (complexity). Instrumentalities (Price, 1984a,b) – interpreted in this paper as physical devices, equipment and instruments, together with the skills to use them[4] – allow testing conditions to be adjusted.

Technological practice draws on science in specific and limited ways that centre on the creation of testing conditions. Instrumentalities can benefit learning processes in two opposing 'directions of fit' (Nightingale 2014:5-8). In learning for science, instrumentalities help to control conditions which are not often repeated or replicated,[5] but need to be highly simplified for identifying patterns and causal explanations (Hacking, 1983; Deutsch 1997). In learning for technology, instrumentalities help to control conditions, where causal explanations are less important[6] but creating new effects and ways of replicating them reliably in more complex environments becomes prime. Such perspectives can be applied to medical innovation, where clinical knowledge is argued to be significantly independent from advances in scientific understanding; this has been referred to as an important 'point of discontinuity with the traditional literature on health technology diffusion' (Consoli and Ramlogan, 2012:315).

Two styles of testing can be used when manipulating testing conditions (Yaqub and Nightingale, 2012). Passive 'testing as validation' involves testing whether similar problems have similar solutions. This can be largely non-theoretical because it is not necessary to know how a technology works in order to know that it does work (Nightingale, 2004:1271). However, it offers little guidance about what to do if tests fail. In such cases, rather than a cycle of conjecture and refutation, active 'testing as experimental intervention' is used to build artificial experimental conditions that create new phenomena to allow theoretical learning (Hacking, 1983).

Since new effects are being created, local variations in practice and instruments can make establishing their reliability difficult: conditions or standards between tests may be too different to be able to observe empirical regularities; accuracy and relevance of observations may be checked with different instruments. More importantly, it can mean that comparison with other effects (new or otherwise) is not possible. With low comparability, the interpretation of testing data in order to eliminate less suitable trajectories becomes subject to intense social negotiation as interests form around particular trajectories. In the case study, we will see how governance structures can either co-ordinate various activities and

[1] The costs of achieving greater clarity about alternatives can be significant: 'Development expenditures accounted for approximately 67% of total R&D spending. These figures, at the very least, suggest great skepticism about the view that the state of scientific knowledge at any time illuminates a wide range of alternative techniques from which the firm may make cost-less, off-the-shelf selections' (Rosenberg, 1994:13). Rosenberg identified this, choosing between alternatives, as being 'what economic analysis is all about'.

[2] However, as mentioned already and as will be explored empirically, an important characteristic that distinguishes medical technology from other complex technology is that safety considerations permeate this process in its entirety.

[3] A more explicit insight into how social visions interact with technological developments can be found in the relationship between diagnosis (Rosenberg, 2002), diagnostic instruments and the establishment of disease causation (pathology) (see Yaqub, 2010). Before vaccine development efforts can take flight, there are some critical elements – namely, a disease and an associated pathogen, and a diagnosis capable of characterising both reliably.

[4] These skills include the development of routines, heuristics, techniques, know-how (as opposed to only know-what), highly specific practices and procedures, experience of what tends to work and what does not (Nelson and Winter, 1982; Pavitt, 1999).

[5] Scientists rarely replicate or repeat experiments, they more often seek to improve and set precedents (Hull, 1988).

[6] 'Technology can exist as an autonomous body of knowledge because it is *possible to know how to produce effects without knowing how those effects are produced'* (Nightingale, 2004 [Nightingale, 2004]:1271, original emphasis).

Please cite this article in press as: Yaqub, O., Testing regimes in clinical trials: Evidence from four polio vaccine trajectories. Res. Policy (2016), http://dx.doi.org/10.1016/j.respol.2016.12.001