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Imagining the future of cell therapies: clinical trials, innovation and the intersection of clinical-academic and commercial visions

This paper examines the role of clinical trials in regenerative medicine innovation, exploring how trials have contributed to translational challenges in the field. Using data from an ethnographic study of UK cell therapy trials I interrogate the institutional framework for clinical trials and the identity-making of trialists. This analysis uncovers a disconnect between a commercially-aligned regulatory framework and a clinical-academic identity apparent in the majority of current trialling activity. These different pathways appear to represent two distinct sociotechnical imaginaries for cell therapies; one which reflects the assumptions of commercial innovation and prioritises economic success, and another which embodies the cultural expectations of academia and emphasises the importance of clinical care. These two imaginaries operate in synergy to some extent but there are significant tensions between them. How and to what extent these tensions are reconciled is likely to determine both the long-term success and the future shape of the field.

Keywords: clinical trials, cell therapies, regenerative medicine, co-production, sociotechnical imaginaries

1. Introduction

Regenerative medicine, like tissue engineering before it, has witnessed increasingly high expectations that remain (as yet) largely unfulfilled. The past two and a half decades have seen significant progress in basic scientific research, such as the full mapping of the human genome, the isolation of human embryonic stem cells and the discovery of the CRISPR process for gene editing. However, these discoveries have not so far been successfully translated into effective, widely used clinical treatments. The halting progress of clinical regenerative medicine is exemplified by the fact only eight advanced therapy medicinal products (ATMPs) have been licensed in Europe to date. Four of these have since been suspended or withdrawn, leaving only four ATMPs currently authorised for use in Europe - all of which are treatments for rare and/or difficult to treat diseases and thus not in widespread use. In 2013 the House of Lords Science and Technology Committee conducted a review of regenerative medicine in the UK which concluded that "the UK is currently underprepared to realise the full potential of regenerative medicine." (HoL 2013). Five years later a House of Commons Select Committee report found that although progress has been made towards a comprehensive strategy for delivering regenerative medicine, there is still "much work to be done" (HoC 2017). Thus although regenerative medicine is generally thought to have great potential, there is a growing recognition that significant obstacles need to be overcome if this potential is to be realised.

One of the main challenges identified in the House of Commons and House of Lords reports was the design and conduct of clinical trials, an issue that has also been highlighted in the academic literature (for instance Gardner et al. 2015; Webster 2013). Clinical trials form a bridge between the lab and the clinic (Webster 2013, 81), and are thus a key element of so-called translational medicine and an important locus of inquiry

for understanding the dynamics of biomedical innovation. Although there are a number of comprehensive quantitative overviews of clinical trials activity in regenerative medicine (see for instance Li, Atkins, and Bubela 2014; Foley and Whitaker 2012)., there has to date been no comprehensive interrogation of the role that the clinical trials process plays in innovation in the field. In-depth case studies of specific trials have been conducted, for instance Hauskeller et al. (2017) explore the role of harmonization and standards in the multi-national BAMI trial, and Will (2011) discusses the challenges and tensions involved in undertaking a stem cell trial in the NHS. Although not focussed specifically on the role of trials in innovation, these studies of individual trials suggest that specific challenges experienced by clinical-academic trials could have an impact on the wider development of the field. This paper builds on this work examining the role of clinical trials in the development of one specific branch of regenerative medicine - cell therapies - in the particular context of the UK. Drawing on Jasanoff's idiom of co-production, and the related concept of socio-technical imaginaries, I explore the role of clinical trials in innovation and investigate how this contributes to translational challenges in the field.

The idiom of co-production argues that scientific knowledge cannot be separated from the context in which it is generated and focuses attention on the role that social institutions play in ordering and reordering our understanding of nature (Jasanoff 2004). Unlike some branches of Science and Technology Studies (STS), which focus primarily on the emergence of science and technology from the day-to-day practice of science, co-production encourages an examination of the political and societal aspects of knowledge governance. It does not take an entirely constructivist or socially-deterministic position, focussing instead on the ways that science and society are mutually-configuring. Jasanoff distinguishes between constitutive co-production, which

focuses on the construction of science and technology, and interactional co-production, which looks more closely at the tensions that emerge as new technologies and knowledge challenge existing practices and regulatory frameworks. This paper draws predominantly on the second of these, which directs attention to the epistemic and socio-political aspects of techno-science and argues that these do not develop separately from or as a result of science and scientific progress, but rather both emerge concurrently in an intertwined, recursive process. This concept is reflected in STS research on clinical trials, such as Keating and Cambrosio's depiction of cancer trials emerging as a new 'style of practice' (Keating and Cambrosio 2007, 2012), and also in much of the STS literature on regenerative medicine, such as Faulkner's concept of 'governation' (Faulkner 2009), which describes the impact of differential and changing regulatory definitions on the development and deployment of Autologous Chondrocyte Implantation. Co-production provides a useful analytical toolkit for the STS researcher, most importantly the four common pathways - or 'ordering instruments' - of co-production that Jasanoff identifies: making identities, making institutions, making discourses and making representations. These ordering instruments are reflected in much of the STS literature on regenerative medicine: for instance, the concurrent emergence of science and the institutions that shape it has been highlighted in research on the UK Stem Cell Bank (Stephens, Atkinson, and Glasner 2011, 2008a, 2008b) and the Cell and Gene Therapy Catapult (Gardner and Webster 2017); different identities - and the tensions between them - are explored in studies of the translational medicine agenda (such as Wainwright et al. 2006; Brosnan and Michael 2014); the making of scientific representations, the ways that these representations travel and the work that they do are explored in studies of the development of standards, norms and shared understandings of cell therapies (Webster, Haddad, and Waldby 2011; Webster and

Eriksson 2008; Eriksson and Webster 2015); and discourses are visible in research highlighting how expectations and promissory narratives about the future potential of cell therapies are deployed to create certain realities in the present (Martin, Brown, and Kraft 2008; Kitzinger and Williams 2005; Brown and Michael 2003).

Jasanoff's recent work has further elaborated the idiom of co-production through the concept of socio-technical imaginaries, which are "collectively held, institutionally stabilized, and publicly performed visions of desirable futures, animated by shared understandings of forms of social life and social order attainable through, and supportive of, advances in science and technology" (Jasanoff 2015, 4). Jasanoff argues that these imaginaries are "both products of and instruments of the co-production of science, technology and society" (19), and that "multiple imaginaries can coexist within a society in tension or in a productive dialectical relationship" (4). Identifying the imaginaries that are shaping an emerging field, and examining the relationship between them, can thus help to explain not only how these intertwined phenomena mutually configure each other, but also why they do so in certain ways, in certain places or at certain times, and not in others - and thus why some potential outcomes materialise in any given context and others do not. Recent research has highlighted the important role that these imagined futures play in the co-production of science and society. In particular, studies have emphasised the role of institutions in elevating some imaginaries above others, allowing these versions to achieve dominance (Jasanoff 2015, 4), and have also described how the making of identities is intertwined with visions of desirable outcomes for science and technological innovation (Burri 2015, 234).

This paper examines the role of two ordering instruments of co-production in cell therapy trials, uncovering two distinctive socio-technical imaginaries that appear to be emerging in regenerative medicine: a commercial model that is implicit in cell therapy

policy and regulation and enacted by the emerging institutional framework for trials, and a clinical-academic model that is articulated in the identities of trialists themselves. I describe the synergies and tensions between these two imaginaries and explore how the dynamic between them has created both opportunities and challenges for innovation, and in the concluding section I consider what this means for the role that clinical trials play in cell therapy innovation, and how the interactions between these two imaginaries in trials is shaping the co-production of science and social order for cell therapies.

2. Methods

The empirical data in this paper is drawn from a mixed methods study of UK cell therapy trials which involved four strands of data collection:

1) Quantitative analysis of a data-set of UK cell therapy trials developed using information from online trial registries, published protocols, the NIHR portfolio database, industry publications, media reports and word of mouth.
2) 17 semi-structured interviews with individuals involved in cell therapy trials. Individuals working on ongoing trials in the UK data-set or on pre-clinical work for trials were identified from the online trial registries entries, word of mouth and the Cell and Gene Therapy Catapult's pre-clinical database. All identified individuals were contacted and asked to participate, and all those who agreed were interviewed – these included clinicians (8), scientific researchers/cell manufacturers (4) commercial cell therapy developers/consultants (3) and trials professionals (2). Five (30%) of the interviewees had some involvement in commercial studies, which is broadly in line with the proportion of UK cell therapy trials that are commercial.
3) An ethnographic case study of one specific trial, including observation, documentary analysis and interviews. The case study site consisted of a

clinical team (involved in surgery and follow-up care), a cell manufacturing facility and a linked scientific research unit. Although for the purposes of anonymity I will not detail the specifics of the treatment or clinical area, these were both relatively typical for the field. The site is, however, one of the more established in terms of the number and scale of trials it has been involved in, which may limit the applicability of the findings.

4) Analysis of secondary sources (such as policy documents and trial protocols. and observation at events in the field (such as conferences, training courses and project meetings).

Quantitative data were analysed using descriptive statistics and qualitative data were analysed using qualitative thematic content analysis, with the ordering instruments of co-production (identities, institutions, discourses and representations) were used as sensitising concepts. This analysis suggested that two different socio-technical imaginaries were emerging through different ordering instruments: a commercial model emerging through the institutional framework of cell therapies and a clinical-academic model emerging through an identity being constructed by the clinical-academic trialists themselves.

To protect the anonymity of research participants the case study trial is referred to by the fictitious name ENABLE and all interviewees are anonymised. Given the number of cell therapy trials in the UK is so small I do not report certain information, such as specific clinical areas or type of cell being trialled, in any context where this could jeopardise anonymity.

3. The institutions of cell therapy trials

3.1 UK policy and regulatory environment

Regenerative medicine policy in the UK (along with many other countries) tends to emphasise both its clinical and its economic potential, as reflected in this relatively typical quote from the House of Lords report: "Regenerative medicine has the potential to save lives and to help support the UK economy" (HoL 2013, my emphasis). The case for investing in cell therapy innovation is thus established on the basis that this will help to achieve the dual policy objectives of improving health and creating wealth. In practice, however, the policy environment in the UK appears to be particularly aligned with wealth objectives - i.e. it predominantly assumes and/or facilitates the commercial aspects of innovation. For instance, one of the most influential actors in the field is the Cell and Gene Therapy Catapult (CGTC), which was established in 2012 (as the Cell Therapy Catapult) with the aim of helping the UK "be a global leader in the development, delivery and commercialisation of cell therapy" (CGTC 2016, my emphasis). The Catapult supports cell therapy innovation by providing developers with clinical, technical, regulatory and business expertise, and has also just opened a centralised cell manufacturing centre which "will be used by companies for the manufacture of late phase clinical trials and initial commercial supply of advanced therapeutic medicinal products including cell and gene therapies" (CGTC 2016, my emphasis).

Another example of a policy initiative which appears to particularly align with a commercial innovation model is adaptive licensing (AL), which is being explored as a means of ensuring patients have access to innovative new treatments as soon as possible. AL is "a prospectively planned process, starting with the early authorisation of a medicine in a restricted patient population, followed by iterative phases of evidence

gathering and adaptations of the marketing authorisation to expand access to the medicine to broader patient populations" (EMA, 2014). In conjunction with AL, risk management systems (RMS) are increasingly being used as a means of overcoming the 'valley of death' economic issues facing developers of innovative biomedical treatments. The UK has been at the forefront of these developments, introducing schemes where, for instance, the manufacturer reimburses drug costs if long term endpoints are not met, or for patients who don't respond to the treatment, as well as cost-limiting schemes such as cost discounts, dose capping and free first cycles to limit the initial outlay on experimental treatments whilst still providing some reimbursement for manufacturers (OECD, 2013). These examples suggest that although regenerative medicine policy rhetoric emphasises both health and wealth, in practice policy initiatives often focus particularly on addressing commercial and economic challenges.

In line with the policy environment, the European regulatory framework for cell therapy trials also appears to be underpinned by a commercial innovation model. The Advanced Therapy Medicinal Product (ATMP) regulations, which were introduced in 2007, mean that the majority (although not all) of the novel cell therapies being developed and trialled in the UK are classed as medicinal products (Abou-El-Enein et al., 2013). There are two key factors that determine whether a cell therapy is designated as an ATMP: whether the cells have been *substantially manipulated* and/or are not being used in their original function (*non-homologous use*). There are four categories of ATMP: tissue engineered products, gene therapy products, somatic cell therapy products and combined products (EMA, 2015). Most cell therapies classified as ATMPs fall within the somatic cell therapy category (see Figure 1).

As medicinal products ATMPs are subject to the same regulatory framework as pharmaceuticals. This means an ATMP must have a marketing or clinical trial

authorisation in order to be used in the clinic (although the Hospital Exemption/specials route, discussed below, does allow for limited use in an individual hospital setting). Clinical trials of medicinal products (CTIMPs) come under the Medicines for Human Use (Clinical trials) Regulations and are therefore much more heavily regulated than non-CTIMPs. They must be approved and inspected by the national competent authority, which in the UK is the Medicines and Health Research Authority (MHRA), and the Investigational Medicinal Product (IMP) must be produced under Good Manufacturing Practice (GMP) conditions. There is an expectation that IMPs will follow a phased approach to trials, being tested first in Phase 1 safety and dosing studies with volunteers followed by Phase 2 studies in a small number of patients and then Phase 3 studies with large samples. This framework mirrors that of pharmaceuticals, which are typically developed commercially (see discussion of commercial CTIMPs below), and contrasts markedly with many other areas of medicine and public health, such as surgery or mental health interventions, where innovation is largely clinically-driven, clinical trials are not regulated by the MHRA, the phased approach is less common and no marketing authorisation is required in order to deliver the intervention to patients.

3.2 Trials activity in the public sector

In contrast to the commercial model which appears to underpin the regulatory and policy framework for cell therapies trials, my research found that in the UK the majority (73%) of trials are currently being undertaken in the public sector. This is in line with the global picture for cell therapy trials (see for instance Li, Atkins, and Bubela 2014; Foley and Whitaker 1012), but it is at odds with the characteristics of clinical trials overall (i.e. trials of all types of treatment). For instance, commercial trials outnumber publicly-funded trials by a ratio of 2:1 in terms of total UK trial activity (Will 2011),

whereas this ratio is reversed for cell therapies. The difference is even more marked when compared to CTIMPs; for instance, data published by the MHRA indicates that commercial trials account for around 95% of Phase 1 CTIMPs and 90% of Phase 2 and 3 studies (MHRA 2019). This is mainly because early-phase cell therapy trials are almost all 'investigator-led', meaning they are run by the clinician/academic developing the treatment rather than by a company. Commercial investment has thus far largely focussed on treatments that have already shown some degree of clinical efficacy, as highlighted by this quote:

> Cell manufacturer working in a clinical lab: "These are still investigator developed products, so they're not coming from pharmaceutical companies. Pharma's buying them, after as early as Phase 1, Phase 2 data, but they're not being developed by them."

This divergence from the typical drug development pathway may be partly because pharmaceuticals are relatively straightforward molecules and can generally be administered to patients in a non-invasive way. In contrast, cell therapies are living organisms which present considerable clinical and scientific complexities and uncertainties when used as a therapeutic agent, and the majority of interviewees felt that because of this complexity the early stages of cell therapy development (including early-phase trials) will always be dominated by academia.

3.3 Policy and regulatory challenges for clinical-academic trials

The unusual preponderance of cell therapy trials taking place in the public sector creates a number of challenges, not least because classification as a medicinal product makes trials extremely expensive to run. Public funding is often insufficient to run these type of trials successfully, as highlighted by the experience of these interviewees:

> Trial manager: "One of the difficulties was we applied for funding to an organisation that was known to support innovative projects … but whose grant-giving ability was … 10% probably, or maybe 20%, of what we actually needed, especially in the new terrain."

> Clinical researcher: "Our first trial came from [charity], and it was very underfunded because again, when I put the grant in there was no regulatory hurdles at all, so it wasn't factored in."

It is difficult to generalise about the exact cost of cell therapy trials (or indeed clinical trials in general) for a number of reasons. Firstly, the cost of commercial trials is commercially sensitive and is therefore rarely available in the public domain. The funding awarded for a publicly-funded trials is occasionally made public, for instance the NIHR (National Institute of Health Research) publicises amount of grants awarded under its clinical research funding streams, but this is far from universal. Furthermore, the amount of the award may not be a good representation of the actual cost of running the trial, either because the grant funds other research as well as the trial or because it does not cover the full costs. Although this makes it difficult to estimate the average cost of a cell therapy trial, a number of interviewees described approximate costs for different aspects of the trial. For instance, these quotes suggest that in addition to the cost of running the trial, the cost of the treatment itself and the ongoing cost of maintaining the research team to run the trials can both be significant:

> Clinical researcher: "You need to pay this treatment which might cost you know £50,000 per patient for a Phase 1 study where at the end of it we're not going to know if it works or not … it's just not tenable."

> Scientific researcher: "We have an outfit at the moment that costs £300,000 a year run, and we have at the moment one year's funding, less - we are funded at the moment until January next year at which point we will disappear if we're not funded any further."

The cost of running large, highly regulated trials of expensive experimental treatments led many interviewees to conclude that commercial involvement will be essential for the successful development of many cell therapies:

> Clinical/scientific researcher: "Ultimately when we move to stem cell therapies it's going to go to a company, because you're never going to sustain it academically."

> Clinician who acted as Chief Investigator for a commercial trial: "We were sort of the pioneers, even though it was a commercial study. And in that sense, it was quite a good one to take forward because we had those resources ... if you were trying to do this academically it would be really expensive."

The implication of the need for commercial funding for trials is that most interviewees felt that commercial considerations will inevitably have a significant influence on the development of these treatments, as demonstrated in these quotes:

> Clinical researcher: "It doesn't matter if you can cure all of your patients, unless someone can make money out of it it's not going to go anywhere."

> Scientific researcher: "It's [the CGTC] clearly set up by a Tory government because their primary aim is actually to generate wealth, but I don't see why that's such a bad thing."

The first of these quotes suggests a grudging acceptance of the economic realities of cell therapy development, but the second suggests a slightly more enthusiastic endorsement of the 'wealth' objectives underpinning current innovation policy. Some interviewees felt that there were in fact significant benefits to commercial involvement in the field, such as academic researchers being able to learn from pharmaceutical companies' expertise in trial design or knowledge of the regulatory framework. Commercialisation thus appears to be tolerated, and in some cases even welcomed, in order to facilitate the development of expensive treatments that are likely to benefit patients.

Despite recognising the economic necessity of commercialising cell therapies, many interviewees felt that aspects of the commercial model were not appropriate for their treatments. For instance, many cell therapies do not fit well with the pathway of undertaking large Phase 3 trials before applying for marketing authorisation, as explained in this quote:

> Cell manufacturer working in a clinical lab: "How would you make it for 200, 400 patients? You couldn't. I don't believe, in the current way that one assesses a drug for a marketing authorisation, that something like a tissue engineered trachea or larynx or oesophagus could get a marketing authorisation."

This interviewee went on to explain that he thought it would be difficult to enforce marketing authorisations for cell therapies with complex production processes, where it would essentially be the process rather than the end product that would be the subject of the authorisation:

> "We've just seen that an Italian company has got a marketing authorisation for limbal stem cell transplants. I don't know how well that's going to stand up, or indeed if it's defensible. To do a limbal stem cell transplant you have to take limbal cells from the good eye, grow them on a substrate and then implant that substrate on the bad eye. So in terms of a licensed medicine, if someone just uses a different substrate it's a different medicine."

These quotes suggest that the trials framework for cell therapies, which mirrors that of pharmaceuticals, may be misaligned with a clinical reality which has more in common with surgical techniques and other complex interventions, which typically follow a different trialling process.

The commercial model underpinning cell therapy policy and trial regulation also appears to limit the effectiveness of many of the initiatives introduced to alleviate the challenges of conducting clinical trials. For instance, there was a notable contrast in

attitudes towards the CGTC between commercial interviewees, who tended to be very engaged with it and positive about its impact, and clinical-academic interviewees, who appeared to find it less relevant to their concerns. For instance, one interviewee suggested that the centralised manufacturing model promoted by the CGTC in order to support trials was not relevant to his tailored treatment that was better suited to local manufacturing (i.e. cell manufactured on site at the hospital rather than in a central facility):

> Scientific researcher: "For the sort of stuff we're doing in [disease area], where it's not just a cell but it's got to grow and integrate and connect, it's a whole package so you can't really take it off the shelf."

This quote depicts the manufacturing model for many clinical-academic cell therapies, which involve a one off manufacturing process (often using a patient's own cells). In contrast, centralised manufacturing facilities such as that being developed by the CGTC tend to use existing cell lines which can be used to treat many patients "off-the-shelf", and are thus unlikely to be viable for such one-off, tailored treatments.

Other interviewees raised additional concerns about the relevance of the Catapult's activities to their trials, in particular suggesting a lack of focus on the institutional challenges perceived to be one of the biggest barriers to cell therapy innovation:

> Clinical researcher: "I'd be interested to know what the stem cell catapult [sic] is doing in this area - I suspect it's not looking at the NHS infrastructure issues."

> Clinical cell manufacturer: "I don't think my department - any hospital department - could reach any level that we'll be able to sell a medicine. So that's what Catapult want isn't it, they're not bothered about the NHS."

Ultimately, most clinical-academic interviewees felt that the CGTC, one of the most important policy initiatives for regenerative medicine, was unlikely to be of much value

to them. Indeed, a number expressed concern that the increased prominence of the centralised model could lead to funds and expertise being diverted away from therapies that require local manufacturing, threatening the long-term future of these treatments.

Just as the CGTC tended to be seen as at best irrelevant by clinical-academic interviewees, so too were the initiatives being pursued to address commissioning and reimbursement challenges for cell therapy trials. There was very little awareness of either adaptive licensing or risk management systems, even when prompted, and notably the only interviewee who made any spontaneous reference to either was a commercial cell therapy developer. The lack of interest in these initiatives is probably partly because they are aligned with the marketing authorisation model that, as already noted, is not felt to be practical or appropriate for many cell therapies being developed under the clinical-academic model. Perhaps most importantly, however, neither of them addresses another reimbursement issue that my research identified as being by far the most important for clinical-academic trials, which is excess treatment costs. Unlike commercial trials, where the company pays for the therapy, treatment costs for publicly-funded trials are met by the NHS. For cell therapy trials these costs can be extremely high, and many interviewees described securing reimbursement as time consuming, uncertain and in some cases entirely impossible. For instance, the ENABLE team had to spend a considerable amount of time securing funding for each trial participant individually, despite the NICE guidelines stating that the treatment should be reimbursed if it was delivered as part of a clinical study. In some cases the funding was denied and the patient could not be recruited, delaying the progress of the trial, and some of these patients had to be withdrawn after randomisation meaning they could not be replaced and weakening the scientific validity of the results. This sort of challenge appears to be common and led many interviewees to voice concerns about the

sustainability of clinical-academic trials. Excess treatment costs are clearly then a significant issue for cell therapy innovation and are entirely unaddressed by current policy initiatives, which predominantly address the reimbursement challenges of commercially-developed cell therapies.

3.4 The role of institutions in imagining the future of cell therapies

Overall, this analysis suggests that the emerging institutions of cell therapy trials, both those specific to cell therapies (such as the CGTC) and those that order knowledge production and innovation in medicine more generally (such as the EMA and the MHRA) tend towards a commercial model of innovation. This aligns with other research that suggests the current regulatory and policy framework tends to marginalise non-commercial innovation. For instance, Sanchez et al. (2013) found that the commercial route can be limiting for academic-initiated trials in the US, and Cuende et al. (2014) argue that the ATMP legislation is not suited to treatments that do not have a commercial interest. The institutions of cell therapy trials are thus implicitly endorsing a desirable future for cell therapies which prioritises the commercial model, and the combined influence and reach of these institutions imbues this vision with considerable power. A good example of the role played by institutions in establishing dominance for a particular socio-technical imaginary is Miller's (2004) description of the Intergovernmental Panel on Climate Change (IPCC), which was instrumental in repositioning climate change from a localised weather phenomenon to a globalised concern. There are echoes of this in the actions of the CGTC, which in positioning cell therapy production as a centralised commercial activity has potentially marginalised those treatments and sites currently using a localised clinical-academic manufacturing model. The difference between this and Miller's description of the IPCC, however, is the fact that the institutional positioning of cell therapies involves the interaction of a

number of different institutions, such as the EMA, MHRA and CGTC. The social order of cell therapies, then, can be understood as emerging from the assumptions and authorities invoked by these institutions, which interlock and mutually reinforce to produce a specific conceptualisation of the future of cell therapies.

4. Identity making in cell therapy trials

4.1 Clinical-academic identity – emphasising knowledge and care over profit

The commercial model underpinning the cell therapy trials regulatory framework is distinctive largely because, unlike pharmaceutical regulation, it is being applied to innovation taking place largely in clinical-academic settings. Some interviewees suggested that academia may be particularly suitable for the early stages of cell therapy development because the combination of clinical complexity and scientific uncertainty make the early stages of innovation inherently unpredictable, as explained in this quote:

> Scientific researcher: "Most advances require an individual who absolutely dedicates him or herself to it and will take the time to do it properly. However much you can say "yes, we're on the verge of a historic advance, it needs a,b,c and d, let us employ people to do a,b,c and d and it will get done" - it won't. It's too complicated and there's too much application to detail, there's too much frustration to be endured."

The implication here is the culture and expectations of academic inquiry may be more suited to this prolonged, uncertain process than a commercial model, which must generate results, and thus profit, relatively quickly. In fact, despite recognising the need for commercial input to cover the costs of expensive clinical trials, many clinical-academic interviewees expressed some discomfort with cell therapies being developed as profit-making products at all. Rather, they emphasised the health objectives of cell

therapy innovation, as exemplified in this comment from an interviewee whose scientific research had recently begun to show promising clinical results:

> Clinical/scientific researcher: "For it to be commercial you have to have something patentable that you can sell ... I would be very happy if no patient ever had to pay a penny for what I had done."

In another similar example one interviewee expressed anger about a treatment that had initially been developed at his hospital before being bought by a company and pushed into "ill-conceived" trials prematurely to expedite the marketing authorisation application. When these trials failed to show efficacy the company abandoned development and patients already receiving the treatment had it withdrawn, despite they and their doctors thinking it was benefiting them. These examples show clinical-academics emphasising that their priority is to treat patients, differentiating themselves from companies which prioritise profit over care, and clearly identifying themselves as 'care-givers' as opposed to 'profit-makers'.

Clinical-academic interviewees also differentiated their identity from the commercial model by emphasising their divergent cultural norms and approaches to knowledge generation. For instance, one interviewee highlighted the conflict between his expectations of transparency and pressure from commercial funders to protect commercially-sensitive information:

> Scientific researcher: "You've got the dreaded confidentiality agreements … companies always have their long spiel of conditions, and the one I always cross out is that any result of work that goes on in my lab or that I have contributed to remains confidential and can only be published with company approval. I'm happy to give six weeks' notice before anything is submitted, but the data is the data, and it's not going to be kept secret."

There were also other aspects of the commercial model that academic researchers

described being uncomfortable with, such as an oncologist who felt that the influx of commercial interest following positive signs of efficacy in CAR T-Cells had made further research in the field more challenging:

> Clinical researcher: "That brings the bad side out - you start seeing people getting protective about reagents, commercial agreements come into place, restricting access to other people, meaning that you have to duck and dive with your process and find alternative suppliers."

The use of the term 'bad side' in this quote highlights the reservation many clinical-academic interviewees expressed about commercial activities, even in some cases voicing outright suspicion as exemplified here:

> Clinical researcher: "Some of the pharmaceutical companies set up trials to stymie their rivals … they do a trial they don't really have any great interest in, but it means there are fewer patients for their rival with a fundamentally new treatment."

The prevalence of these views amongst clinical-academic interviewees suggests their involvement with commerce represents at best an uneasy truce between what they perceive as two fundamentally different perspectives on how research should be undertaken and communicated, as well as what the priorities of that research should be.

4.2 Trials as a challenge to the clinical-academic identity

Identification as a care-giver was used by some clinical-academics to question the relevance of restrictive clinical trial requirements designed for products being developed by 'profit-making' companies, as expressed by this interviewee when describing his response to being challenged about 'cherry picking' data from a trial rather than only reporting pre-specified outcome measures:

> Clinical/scientific researcher: “People have this huge suspicion of all of this, and you say well there’s nothing wrong with it - I’m not trying to sell a product.”

Clinical-academic researchers also tend to lack experience of Clinical Trials of Investigational Medicinal Products (CTIMPs), in fact despite all being responsible for at least one cell therapy trial none of the clinical-academic researchers I interviewed were trial specialists, and only one had any prior experience of trialling at all. The investigators setting up and running cell therapy trials are thus unfamiliar with regulatory requirements and lack expertise in trial design, meaning they are less likely to use complex or innovative methods that could make trials more efficient. Many interviewees felt that their inexperience had hampered the process or resulted in aspects of the trial being more difficult than necessary, as exemplified by this quote:

> Clinical researcher: “I think because it was such a big step, and so unfamiliar to me, I did what a lot of people do in those circumstances and just sort of made it a bit too complicated.”

This inexperience is compounded by the fact that the regulatory demands of running a CTIMP do not align well with the priorities and practices of academic research. For instance, one interviewee highlighted how the issues that trials need to address do not tend to be those that academics want to focus on:

> Clinical/scientific researcher: “A lot of the questions are very boring and they’re not scientifically very interesting. But ultimately they will determine whether your therapy works.”

In another example a clinician voiced his concern that the scientific researcher involved in his trial might find her career adversely affected by her involvement because trials are less likely than basic scientific research to generate the ‘significant’ findings needed to publish in high impact journals. It seems, then, that despite clinical-academic

investigators being integral to the trialling process for cell therapies, this process is both unfamiliar to them and can conflict with their own priorities and motivations for undertaking research.

Concerns about the relative distribution of risks and benefits appears to be another area of tension between the clinical-academic identity and the commercial model of innovation in trials. In particular interviewees were concerned that the financial burden (and risk) of undertaking pre-clinical development and early-phase trials is largely being borne by the public sector. The current model of early trials being largely investigator-led provides a cost-efficient way for companies to identify treatments which have real clinical potential, as exemplified in this quote:

> Cell manufacturer working in a clinical lab: "Pharma see it as a new paradigm that saves them money - it de-risks the process if someone in academia is doing an early phase trial and shows efficacy. One in a thousand drugs gets through to Phase 1, but someone has done your Phase 1 and you're buying it when you've got safety data and you've got some efficacy."

The use of the phrase 'de-risk' is important here, because of course the risks of undertaking early trials have not been eliminated in this model, they have simply been transferred from the commercial to the public sector. The public sector does not necessarily have a corresponding share of the potential benefits of innovation, however, because once bought by a company a cell therapy becomes a product that must be paid for - and the costs are likely to be high. For many interviewees this was a significant concern for the future, articulated here by a researcher involved in the development of an expensive cell therapy:

> Clinical/scientific researcher: "My greatest anxiety is we develop a stem cell therapy that works incredibly well, we think we've got a wonderful treatment to offer people with [disease] and then suddenly you discover we can't afford it."

This quote encapsulates the fundamental difficulty at the heart of cell therapy innovation: the clinical-academic and commercial models can support each other in order to both improve health and generate wealth, but they also have different priorities which can compete with and potentially impede each other.

4.3 Hospital exemption: an alternative model for clinical academic innovation?

The challenges caused by ATMP classification can be avoided in certain circumstances, because although ATMPs generally require either a marketing or clinical trial authorisation the legislation allows for the exemption of treatments that are "prepared on a non-routine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient" (Cuende et al., 2014). Inevitably, this exemption has been interpreted differently by the various member states, with the terms 'custom-made', 'industrial process' and 'non-routine' all being open to interpretation. In the UK, therapies must be prepared within the same hospital to be eligible under what is known as the Hospital Exemption (HE), and these products do not require a QP to sign them off (Cuende et al., 2014). Although providing the least restrictive of the regulatory options for producing cell therapies, at the time of writing there was only one site in the UK known to be producing cells under HE. It does not, therefore, appear to be a significant route for the development of such treatments, a conclusion supported by the fact that many interviewees had not heard of it.

The relative obscurity of HE in the UK may be partly due to the existence of an alternative - the so called 'specials' route, which provides a similar framework for the delivery of medicinal products without a marketing authorisation (MHRA, 2015). This

is more restrictive than HE in some ways, for instance the requirement for a QP to sign off batches of product. However, a specials licence provides greater scope for the delivery of cell therapies, because the use of the product is not restricted to the hospital where it was prepared, and indeed it makes it possible to import and export unlicensed medicinal products (Cuende et al., 2014). There is no centralised data available on the number or type of cell therapies being delivered under specials licences, or how many patients have been treated. However, there are a total of 26 sites with licences to manufacture cell therapies for human use (MHRA, 2015), and a number of interviewees described such cells being in regular use.

It appears, then, that although it is not possible to quantify exactly how many cell therapies are delivered to patients using hospital exemption or specials licences (referred to hereafter as HE for brevity), it is certainly a significant route for the delivery of cell therapies in the UK. It does not, however, appear to offer clinical-academic innovation a viable alternative to clinical trials and marketing authorisation. Most interviewees felt that HE was only appropriate for treatments that already have evidence of efficacy, or as a pre-cursor to a trial, rather than as an alternative route. For instance, this interviewee explained that he had moved straight to a clinical trial rather than considering HE because he felt that the collection of evidence from 'proper' trials was important for the scientific development of the field:

> Clinical researcher: "It's not good science really because what we really need, especially in cell therapy, are properly designed clinical trials to be executed and completed. And we still see even now in my field some really uber-eminent people publishing case reports and series, and two or three patients in the New England Journal of Medicine. And they are remarkable results, but that's not a proper clinical trial."

This quote suggests scepticism about the evidence generated by individual clinical cases conducted HE, which is reflected in another concern raised about whether evidence generated through HE would be accepted by quality journals or could be used to support further clinical development:

> Clinical researcher: "We thought about specials licences and all sorts of other ways round it, but at the end of the day we knew we wanted to publish our data. And if we didn't go through the regulatory route we wouldn't be able to publish it, or we certainly wouldn't be able to use those data in terms of the next phase of our work … I think there was some nagging doubt that had we not gone through the regulatory process would it disqualify our publication from that journal."

The fact that so many interviewees were in favour of structured trials thus appears to be motivated not only by the belief that trials generate more robust evidence than clinical experience alone, but also by an awareness that trial evidence is more likely to be aligned with the expectations of key decision makers in the future.

As well as concerns about the validity and acceptability of the evidence generated through HE for experimental treatments, my findings also suggest that it may not always be a sustainable alternative to commercialisation for more proven treatments. For instance, although the team at the ENABLE trial site were keen to continue developing their cell therapy within the hospital, they were not enthusiastic about applying for marketing authorisation. There appeared to be a number of reasons for this, perhaps most importantly the fact that they felt a marketing authorisation would require them to produce the treatment on demand for other sites, which did not fit with their production model. There also appeared to be a lack of desire within the hospital trust to commercialise the treatment, and the collaborative way that the team were working with other sites to further develop the manufacturing process also did not appear to lend itself

to the marketing authorisation model. However there was uncertainty and anxiety in the team about whether this was the best long-term approach, because of concerns that if they did not have marketing authorisation for their treatment and another (likely commercial) provider ever did get authorisation that they would find themselves unable to continue producing it for their patients.

4.4 The clinical-academic narrative of cell therapy innovation

The ENABLE team's approach appears to encapsulate the clinical-academic identity, and the desirable future it envisions. This identity emphasises and draws authority from the clinical-academic role as 'care-giver' as opposed to 'profit-maker', drawing out the tensions that clinical-academic researchers perceive between these two interests. These tensions reflect important practical, cultural and moral divergences between the two spheres. At a practical level, the clinical-academic identity is characterised by a lack of the financial resources, infrastructure and expertise required for undertaking highly-regulated drug trials, and it tends towards a localised manufacturing model that does not lend itself to commercialisation. On the other hand, it is presented as having strengths that the commercial model lacks, particularly in the way that individual or small teams of clinicians and academics are able to dedicate themselves to an uncertain and prolonged innovation process which is ill-suited to the commercial model. Culturally, the clinical-academic identity promotes a collaborative and transparent innovation processes and is often resistant to or ambivalent about pursuing the commercial aspects of cell therapy innovation, such as intellectual property or marketing authorisation. From a moral perspective, clinical-academic researchers often express distaste for commercial priorities taking precedence over clinical need, and voice suspicion about restrictive or even underhand commercial practices. In the context of these tensions it is unsurprising that the clinical-academic identity is distinguished by significant

reservations about the impact of commercialisation on cell therapy innovation, even as individual researchers tend to understand and accept its importance from an economic perspective.

5. Discussion

These findings suggest a disconnect between a commercial model of innovation enacted by the institutions of cell therapy trials and a clinical-academic identity that underpins the conduct of the trials themselves. The intersection of the academic and commercial spheres is of course not in itself unusual, indeed the triple helix innovation model adopted by most Western economies actively fosters this approach to innovation in general (Etkowitz 2008), and regenerative medicine specifically (Salter 2013). What appears to be distinctive for cell therapies, however, is the extent to which the clinical-academic sphere is undertaking clinical trials of medicinal products that are usually conducted primarily by companies. These trials are more challenging for clinical-academic settings than investigator-led trials in other clinical areas, such as surgery, which are generally be non-CTIMPs and thus subject to much less stringent regulation and oversight. A regulatory regime that has traditionally been applied to drugs being developed and trialled by pharmaceutical companies is thus now being applied in clinical-academic settings, creating a distinctive configuration of clinical-academic and commercial interests in the field of regenerative medicine.

To some extent the commercial and clinical-academic models appear to have complementary strengths that mitigate the limitations of the other. For instance, academic research is particularly suited to the uncertain early phases of cell therapy development, whereas commercial innovation can provide trials expertise and funding that the public sector lacks. These synergies are reflected in the fact that even

commercial cell therapy trials tend to involve SMEs and/or university spin-outs (such as Videregen ReNeuron) rather than multi-national pharmaceutical companies. These companies can face similar challenges to the clinical-academic trials, and the individuals involved can have strong clinical-academic links. The distinction between commerce and care which is emphasised by many clinical-academics may thus in actuality be more rhetorical than real. Nevertheless, commercialisation can be a double-edged sword for clinical-academic innovation: commercial input is important because of the high costs of development, but this means that commercial considerations will inevitably shape this development, potentially being prioritised over clinical potential and need.

The differences between the clinical-academic and commercial models can be understood in practical terms, such as their relative levels of trials expertise or access to funding. However, my findings also suggest that these two models, whilst relying on and supporting each other to some extent, also reflect different visions of what the future of cell therapies could, or should, look like (see Figure 2 for an overview of the key differences between the two). The commercial model envisions a desirable future in which cell therapies are developed competitively by companies, distributed universally on an open market under marketing authorisation, and above all else generate a profit. Conversely, the clinical-academic model envisages a future in which cell therapies are developed collaboratively in a clinical setting, distributed at a local level through hospitals, and above all else benefit patients. In this way, then, the clinical-academic and commercial models can be understood as articulating two different socio-technical imaginaries for cell therapies, in that they "encode not only visions of what is attainable though science and technology but also of how life ought, or ought not, to be lived." (Jasanoff 2015). Supported as it appears to be by regulation and policy, the commercial

model could perhaps be understood as the dominant imaginary, with the clinical-academic model representing an alternative, heterodox vision. It appears to exist in the liminal spaces of the dominant commercial model; lacking a cohesive institutional framework it struggles to gain or retain traction, despite setting the agenda for the scientific and clinical aspects of cell therapy innovation.

The synergies and tensions between academic research and commercial interests in medical innovation are well-documented in the social science literature, and a number of studies have described the various configurations and reconfigurations of commercial and public interests in clinical research (see for instance Addison 2017; Kohli-Laven et al. 2011). In this context, my findings suggest that cell therapy trials create another such distinctive configuration of the public and private sector. By undertaking early-phase CTIMPS that are more usually run commercially, clinical-academic research is not just engaging with commerce it is actually operating in the commercial sphere in ways that are new and unfamiliar to many of the individuals involved. The acceptance of the commercial socio-technical imaginary by clinical-academic researchers is clearly an uneasy one, however, and this is exacerbated by the perception that the public sector is shouldering the majority of the cost of early stage clinical trials in cell therapies, whilst the commercial sector stands to reap the most benefit. Will (2010) argues that the Clinical Research Network model has essentially led to the NHS acting as a Contract Research Organisation for commercial research, and my findings suggest that for cell therapies this model is heightened and extended. The public sector is not only providing the research infrastructure for early-phase trials, it is also designing, managing and financing these trials. What this means, of course, is that much of the risk is transferred to the public sector, which is undertaking expensive trials but will not benefit economically if these trials are successful. The unspoken assumption behind this is that

these trials will ultimately benefit patients, making this an appropriate use of public funds. But if these treatments become either unavailable (because companies choose to withdraw them), or unaffordable, this implied contract breaks down. This highlights the extent to which commercial and clinical-academic imaginaries, whilst in many ways synergistic and inter-dependent, also represent different, and potentially conflicting, priorities.

One of the most useful aspects of using socio-technical imaginaries as an analytical tool is that it highlights the way that "space and social order are co-produced in part through the spread of ideas and practices - and indeed ideologies - across time and territories" (Jasanoff 2015, 22). In the case of cell therapies, the commercial imaginary enacted through the clinical trials framework appears to severely constrain the 'space' available for the alternative, clinical-academic imaginary to spread. The demands of the commercially-aligned clinical trials framework place a considerable burden on clinical-academic investigators, and although the hospital exemption does provide an alternative framework for developing cell therapies the ENABLE team's concerns highlight the uncertainty and insecurity of this approach. In the current regulatory framework marketing authorisation effectively 'trumps' HE, which essentially means that clinical-academic innovation is always at risk of being extinguished by commercial providers. The absence of a secure, structured alternative to the CTIMP-marketing authorisation pathway thus limits how far clinical-academic cell therapy innovation can progress. This is not to say, however, that the heterodox imaginary is destined to be eradicated: whilst the commercial imaginary has a powerful institutional framework, the clinical-academic imaginary is embedded in the identities and day-to-day practices of the people undertaking trials. Both imaginaries thus have a strong cultural foundation, and whilst the tensions between them are clearly a significant cause of the challenges experienced

by cell therapy trialists, they also appear to have symbiotic strengths and weaknesses which may make them indispensable to each other.

6. Conclusion

The dynamic between the two imaginaries described in this paper appears to have both productive and conflicting aspects. Commercial and clinical-academic involvement are both important elements of the innovation process, with a commercial model being necessary because of the high costs of developing and producing these treatments, and clinical-academic input being vital because of their scientific and clinical complexity and the uncertainties involved in their development. These two models do not just represent complementary aspects of innovation, however, they also represent different visions of the desirable future for cell therapies. The fact that the commercial desirable future is firmly embedded within current regulation and policy means that the clinical-academic imaginary is currently somewhat marginalised, despite being the driver for the majority of current trialling activity. By implicitly prioritising the commercial imaginary, the trials framework is thus promoting certain normative assumptions about what we as a society think the future of these treatments should look like. It also makes this imagined future more likely to come about, by favouring innovation in products that are most likely to have commercial benefit rather than those with the most clinical promise, and by increasing the challenges faced by clinical-academic innovation. Thus, although there are clearly areas where the two socio-technical imaginaries for cell therapies converge, or complement each other, there are also significant tensions between them.

Jasanoff (2005) argues that in modern knowledge societies democratic negotiation takes place not only, or even primarily, through the overtly democratic or political processes

such as elections. Rather, normative debates about how societies should be run and epistemological debates around how they understand themselves take place in multiple, often hidden places: in the decisions of regulators, in the wording and application of laws, in the allocation of funding and in the production and interpretation of evidence, to name but a few. In this context, the extent to which the tensions between the clinical-academic and commercial imaginaries can be reconciled, allowing them to support rather than constrain each other, not only has significant practical implications for only innovation in the field, but also has important normative implications concerning what we as a society think the balance between these two imaginaries should be, and thus what the future of these treatments should look like.

WORD COUNT: 9115

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FIGURES

Figure 1: Definition of Somatic Cell Therapy (EMA, 2015)

> (a) contains or consists of cells or tissues that have been subject to substantial manipulation so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered, or of cells or tissues that are not intended to be used for the same essential function(s) in the recipient and the donor;
> (b) is presented as having properties for, or is used in or administered to human beings with a view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic

Figure 2: Comparison of clinical-academic and commercial models of cell therapy innovation

	Clinical-academic	**Commercial**
Main priority	Clinical efficacy	Economic potential
Approach to knowledge	Transparency and collaboration	Lack of transparency / protection of intellectual property
Manufacturing model	Local / tailored	Centralised / off the shelf
Regulation of trials	Minimal regulation	Highly regulated
Trials process	One-off trials and/or HE use followed by adoption into clinical practice	Phases 1-3 followed by marketing authorisation application