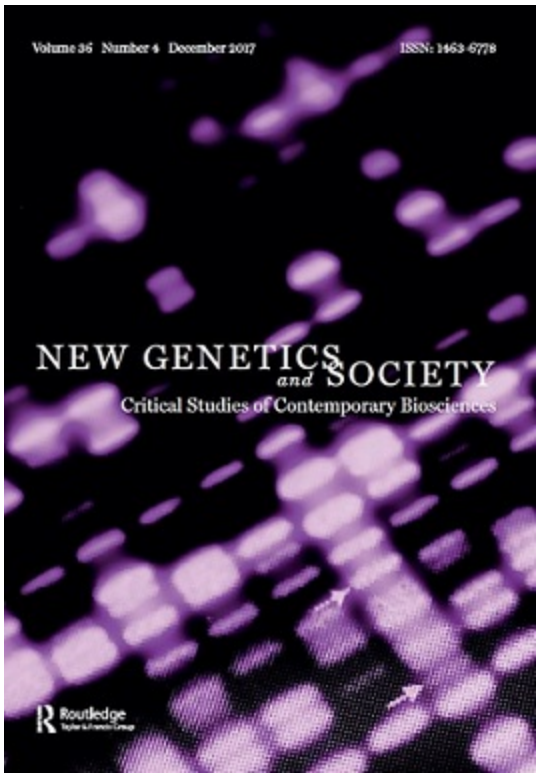

Exploring 'quality' in cord blood transfusion: uncertainties, bionetworks, and collaborations

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22nd March 2022

Dear Managing Editor,

Author Response – CNGS-2021-0002

Thank you for the opportunity to revise and resubmit our manuscript titled "Exploring 'quality' in cord blood transfusion: uncertainties, bionetworks, and collaborations" for publication in *New Genetics and Society*.

We would like to formally convey our gratitude to the two anonymous Reviewers for their thoughtful and considered comments, and importantly, for their time and support to continually enhance our paper. In light of their comments, we have made minor revisions to the manuscript.

In response to Reviewer's 1 comments, we have:

- Added papers authored by Beltrame that refer to jurisdictional disputes, and acknowledged and made reference to this work in the manuscript.
- Removed reference to Esposisto and communitas and immunitas.
- Added text to acknowledge the difference between professional groups and varies stakeholders and their understandings surrounding 'quality' cord blood.

In response to Reviewer's 2 comments, we have:

- Added Table 2 to make clear the differences between the consultants' approaches to decision making
- Moved the paragraph that outlines the differences between consultants' approaches to decision making earlier in the Discussion section and linked the Table to this paragraph to reinforce the differences between the UK and Japanese.
- Added additional references to support boundary building around clinical and scientific that have been witnessed and reported in other aspects of donation and stem cell research.

We have also reviewed and amended the formatting of the list of references to ensure that it is compliant with journal author guidelines.

We thank you for considering our manuscript for publication within *New Genetics and Society*.

Yours sincerely,

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Exploring 'quality' in cord blood transfusion: uncertainties, bionetworks, and collaborations

Abstract: Umbilical cord blood unit (CBU) 'quantity' continues to grow internationally, whilst cord blood transplantation (CBT) 'quality' remains poorly defined and subject to uncertainty. CBT 'quality' is affected by both the product (i.e. CBUs) and CBT processes, with 'best practice' varying across countries. To improve overall CBT 'quality', we need to better understand the uncertainty associated with CBUs and CBT processes, and how staff manage it. In this qualitative study, we conducted in-depth semi-structured interviews with individuals working in CBT in UK and Japan. We found that understanding of CBT quality by the cord blood community, is underpinned by the quality of the CBU, the expertise and collaboration of scientific and clinical stakeholders, trust in collection and testing processes and international accreditation. Importantly, we found that local and individual experience is used to manage uncertainty within CBT, and we propose that selection guidelines should acknowledge the extent of uncertainty in decision-making.

Keywords: cord blood transplantation, cord blood quality, uncertainty

Introduction

Since Gluckman's first successful trials in Fanconi's anaemia in 1988, umbilical cord blood units (CBUs) have become an important source of haematopoietic stem cells (HSCs) for various haematological conditions (Gluckman et al. 1989). CBUs can act as a source of HSCs for patients who would otherwise struggle to find a bone marrow match, such as those from ethnic minority communities, and those without genetic siblings (Dessels, Alessandrini, and Pepper 2018; Hough et al. 2016). CBUs require less accurate Human Leukocyte Antigen (HLA)-matching to be useful for a wider population compared to bone marrow (Dessels, Alessandrini, and Pepper 2018).

Furthermore, CBUs are already physically stored when the decision is taken to use them for transplant, whereas there is a *"necessary and time-consuming"* gap for bone marrow to be harvested from matched donors (Brown, Machin, and McLeod 2011). Hence, the rapidly available and 'off-the-shelf' nature of CBUs for a broad patient population is particularly attractive in clinical emergencies and when procurement becomes difficult, such as during the SARS-Cov2 pandemic (Kindwall-Keller and Ballen 2020).

Yet, cord blood transplantation (CBT) can still be considered a novel technology. It accounted for only six per cent of allografts in the UK, and the number of CBUs shipped globally fell by nearly one third between 2012 and 2019 (World Marrow Donor Association 2020). Conversely, the number of internationally banked CBUs has continued to rise resulting in a growing surplus. The standards for CBUs to be acceptable for transplantation have developed over time, which is captured in the work of Eurocord; a cord blood registry and study group that works with banks and registries to analyse outcomes of CBT (http://eurocord.org/index.php). The exact number of CBUs currently stored that would be acceptable for transplantation today is unknown. These evolving standards reflect the uncertainties and complexities surrounding determining 'quality' with CBUs. Consequently, there have been calls from within the cord blood community to focus upon and better understand defining and improving 'quality' in CBUs (Querol et al. 2010). To date, there has been limited exploration of the notion of 'quality' in CBT that goes beyond the scientific community, or that adopts a qualitative approach to the topic.

'Quality' Cord Blood

The notion of 'quality' in cord blood is rarely complicated in the existing literature, and

instead an objective depiction of the 'scientific' characteristics are presented. CBT 'quality' can be split in to intrinsic CBU product 'quality', relating to the biological factors of the CBU, and process 'quality', which includes collection, processing, procurement and treatment. For clarity, an overview of CBT processes is shown in Figure 1. Collection 'quality' and the associated ethical conflicts of CBU collection have been discussed elsewhere (see Machin 2016) and will therefore not be discussed further in this paper. Instead, we will summarise current understanding of CBT 'quality' in the literature and in clinical practice.

The concept of CBT 'quality' is defined by international standards and national guidelines. International standards were first created in 2000, when the International NetCord Foundation (NetCord) and the Foundation for the Accreditation of Cellular Therapy (FACT) first collaborated as NetCord-FACT. These standards cover all areas of CBT; NetCord-FACT provide accreditation for banks who meet these 'quality' standards, providing some level of international standardisation of CBU banks. The most recent standards enact CBU testing requirements for banks, which can be split into safety requirements (e.g. viral screening, ABO/Rh) and markers of CBU 'quality' (NetCord-FACT 2019). These 'quality' markers include CD34+ count, Total Nucleated Cell (TNC) count, TNC viability, CD34+ viability, Colony Forming Units and HLA typing. National guidelines differ across countries and often prioritise different measures of CBU 'quality'. Whilst findings from Eurocord have led to the modification of cell dose thresholds to improve CBT outcomes, uncertainty remains and varies across different professional domains and stakeholder groups regarding the most accurate 'quality' measure, minimum acceptable cell counts for CBT success and how best to perform CBU selection (see Table 1 for key 'quality' markers). However, these are 'known unknowns' and conscious debate on these issues is ongoing, both in the

literature and between different nation's guidelines (Barker et al. 2011; Dehn et al. 2019; Hough et al. 2016; Politikos et al. 2020; Rich 2015; Shaw et al. 2009).

Quality in laboratory medicine has been defined as "*the guarantee that each activity throughout the total testing process is correctly performed, providing valuable medical decision-making and effective patient care*" (Lippi et al. 2013). Although the quality of analytic processing has improved significantly throughout laboratory medicine, pre- (i.e. CBU collection) and post-analytical (i.e. CBU storage) stages remain targets for improvement. This is primarily by identifying quality indicators (Lippi et al. 2013). Yet, intrinsic CBU product, CBU process 'quality', and its' impact on clinical outcomes, remains poorly understood in the literature. For example, the impact of the collection bag material and the maximal appropriate duration of CBU storage is *"still not defined"* (Querol et al 2010), highlighting inadequate understanding surrounding quality indicators in post-analytical CBU processing. Studies report no differences in clinical outcomes relating to the processing methods used by different banks (Ballen et al. 2015; Nikiforow et al. 2017; Saccardi et al. 2016; Santos et al. 2016). Detailed descriptions of processing methods are provided in NetCord-FACT standards, although the impact of variation within such methods remains unknown, and further 'unknown unknown' factors may yet exist undiscovered.

These 'unknowns' when contemplating CBT quality highlight *"the limitation of our knowledge"* and the epistemic uncertainty that results (Indrayan 2020). Epistemic uncertainty, due to an incomplete knowledge of the particular system in question, is ubiquitous within medicine, particularly when considering technological advancement and novel treatments such as CBT. Process 'quality' has arguably been discursively and pragmatically constructed by prominent actors, including NetCord-FACT and those in transplant centres drawing on their clinical experiences and as such varies across

professional domains. Within the UK CBT community, governmental (Department of Health's Stem Cell Strategy Oversight Committee) and medical groups (British Society of Blood and Marrow Transplantation Cord Blood Working Group) have led stakeholders to form a clear and unified narrative of the current 'state of play'. In turn, stakeholders steer clinical practice and research forming a *"collective production of (un)certainty";* presenting what is known about CBT with confidence and highlighting what needs to be known for practice to develop and advance (Cambrosio et al 2006; Moreira et al 2009).

Yet, CBT operates within a complex bionetwork, which is defined as consisting of a *"plurality of actors…working across geographical spaces, regulatory regimes and social institutions"* (Sleeboom-Faulkner and Patra 2011). CBT product and process 'quality', and their associated uncertainties, form only the content of the CBT bionetwork; the diverse range of stakeholders add further complexity to narratives surrounding CBT. In current CBT practice, different 'truths' seem to simultaneously co-exist, as shown by variation between national guidelines and local selection policies (Barker et al. 2011; Hough et al. 2016). Consequently, what determines quality in one domain such as registries and biobanks, may not satisfy the criteria for those in transplant centres. The interplay therefore between national and international interest groups, including their differing recommendations, motives, and relationships, creates a "*shifting landscape*" (Williams 2018). The aims of these stakeholders may not overlap and networking means that each player's role becomes blurred (Chang 2016). This can frustrate transplant centres as they must put these differing recommendations into practice and evolve in response to the "*shifting landscape*" (Williams 2018). In addition, transplant centres "*have very little control over what happens in other jurisdiction(s)"*; NetCord-FACT standards allow significant variation within acceptable

practice, giving transplant centres little control over the 'quality' of processing methods (Brown, Machin and McLeod 2011). Thus, a successful CBT bionetwork relies on collaboration between stakeholders, including transplant centres; to build trust, increase confidence in policy and ultimately navigate the complexity of the CBT bionetwork.

Collaborations and Networks

For collaborations to be successful, professional boundaries need to be transcended, which can lead to a loss of autonomy for all those involved (D'Armour et al. 2005; Freeth 2001). Furthermore, complex relationships can form between the different occupational groups, sometimes reflecting the implicit power imbalances that can emerge when working collaboratively (D'Armour et al. 2005; Gachoud et al. 2012). In response to the perceived loss of power and autonomy, informal processes can form surrounding the interactions between professional groups, which facilitate the continuation of the collaboration as well as upholding professional boundaries (Heldal 2010). Through these informal processes, we can observe professional "*territories of care*", each with their own priorities and patterns of working (Hardey et al. 2001) and distinct areas of knowledge and practice (Langan-Fox and Cooper 2014). Knowledge is deemed central to professional control (Abbott 1988), and therefore 'discursive' battles can result as occupational groups attempt to claim or maintain their jurisdiction and expertise (Covaleski, Dirsmith and Rittenberg 2003). One occupational group can attribute characteristics to another group in order to distinguish themselves more favourably, for example work activities can be portrayed as 'scientific' or 'non-scientific' (Gieryn 1983). Such discursive boundary work (Gieryn 1983) observed in the context of CBU banking (see Machin, Brown and McLeod 2012) has similarly been explored within the CBT community. Beltrame (2020a; 2020b) addresses the

jurisdictional disputes in relation to the practices of valuing the clinical quality of cord blood.

Collaborative networks have been key to CBT since its inception, with national and international banking and matching networks including Eurocord and National Marrow Donors Association (Brown, Machin and McLeod 2011). Nations and their donors have often been viewed as altruistic participants, donating 'gifts' to an inclusive and collaborative community (Brown, Machin and McLeod 2011). Whilst the majority of CBT practice exists within a public international community, notable exceptions are private CBU banks (where individuals store CBUs for their own familial use only) and nations with a self-sufficient CBU supply, such as Japan (who generally do not engage with international CBU trade). Different nations, such as Japan and the UK can therefore hold different positions within the CBT bionetwork, often influenced by culture and strategy.

CBT in Japan and the UK

Japan were early adopters and innovators in CBT, creating a CBT committee in the mid-1990s and national bank network in 1999 (Takanashi et al. 2011). This coincided with the Japanese government's Millennium Project, part of an expansive plan to become *"the scientific and technological nation"* (Fukushima 2016). Contradicting the international trend, Japan has continued to perform more CBTs year-on-year (Japanese Red Cross Society 2021). Underpinning the Japanese successful CBT programme are a strong national collaboration via the Japanese Cord Blood Bank Network, and a prioritisation of scientific rather than political goals. The potential damaging influence of politics in science is reflected in the failed Japanese Protein 3000 Project, which had significant political involvement and therefore struggled with high societal expectations

of the scientific achievements resulting from political over-promises (Sleeboom-Faulkner 2011). For Japanese scientists then, widespread collaboration, or high political involvement could equate to unrealistic public and professional expectations of science, and a decreased ability to exert control over a project. That said, the importance of CBT for the country was reflected in 2014, when the Act for Appropriate Provision of HSC to be Used in Transplantations was enacted in Japan, which aimed to increase efforts to "*ensure the quality of CB(Us) used in transplants*".

The UK government were slower than the Japanese government in their uptake and focus on cord blood, with a national strategy on CBU banking not developed until 2010. Data showed that 90% of CBUs given to UK patients were imported, with each unit being *"prohibitively expensive"* (Brown, Machin and McLeod 2011). The UK government promoted collaboration between the main UK CBU banks Anthony Nolan and the National Health Service Blood and Transplant agency (Williams 2015). The interests of these two CBU banks were aligned as a result of financial incentives, which prompted a switch from international 'competition' to national 'collaboration' (Williams 2015). As a result, the UK planned to increase their domestic CBU supply with the hope of achieving self-sufficiency (All Party Parliamentary Group on Stem Cell Transplantation 2012; UK Stem Cell Strategic Forum 2010). In 2012, the matter of quality CBUs arose, when the UK All Party Parliamentary Group on Stem Cell Transplantation proposed a best practice tariff to reimburse hospitals for securing *"high quality collections"*. Given the high level of imports and HLA diversity of the UK population, as with most Western countries, complete self-sufficiency has been deemed to be an unrealistic target (Williams 2015). Japan however is considered unique when described as the *"only country [that can be CBU self-sufficient] … because they're such a homogeneous group"*; in 2008, Japan did not import a single CBU (Brown, Machin

and McLeod 2011). As such, Japan has sat outside the international CBT community and appears immune to international fluctuations in cord blood policy or supply (Brown and Williams 2015). Japan and the UK hold vastly different positions within the CBT bionetwork, particularly their national policies on CBT. Their positions are affected by (geo)politics, history (of scientific advancement), culture and ethnic diversity within each country. Consequently, their definitions of CBT 'quality' may differ.

To date, there has been limited primary qualitative research on CBT 'quality'. A focus on CBU 'quality' (rather than 'quantity') and qualitative understandings of CBT generally may support progress within CBT (Querol 2010). In this paper, we therefore aim to broaden understandings surrounding 'quality' within CBT and promote wider discussion within the literature. We propose CBT 'quality' (and its' individual elements) cannot be accurately captured within singular definitions. Instead, descriptions of 'quality' may be discursively constructed from differing perspectives within the "*shifting landscape*" of the CBT bionetwork (Williams 2015), and are therefore vulnerable to the ubiquitous epistemic uncertainty within CBT practice. It is noteworthy that the matter of 'quality' CBU from the perspectives of those working in transplant centres have rarely been explored in-depth. We suggest that transplant centres act as "*regime(s) of truth*" describing the situation as it is, rather than how it should be in ideal circumstances, making their perspective of particular interest (Martin, Brown, and Turner 2008; Moreira and Palladino 2005; Williams 2015). In this paper, we provide insight into how some stakeholders working in transplant centres understand CBT 'quality' in practice. We explore how trust, collaboration, uncertainty, expertise and experience can inform and shape the varying perceptions of 'quality' of these stakeholders. We conclude that the cord blood community use their own experience, and that of trusted colleagues, to manage uncertainty within CBT to varying extents. In

turn, the role of experience, expertise and collaboration in decision-making is affirmed and arguably valued.

Materials and Methods

The study took place at hospitals in Japan and the UK during July 2014 and July 2015. Participants were recruited because of their close and prominent involvement in CBT. This included two transplant consultants from different sites in the UK, three transplant consultants from three different sites in Japan and four other transplant team members, all of whom are from the same site as UK Consultant 2 (a tissue typer, a transplant co-ordinator, a lab manager and a clinical nurse specialist). Recruitment was via an email invitation disseminated by departmental secretaries and participation was on a voluntary basis. Nine in-depth semi-structured interviews were conducted; each lasting between 30 and 90 minutes. Consent was gained prior to interview. Institutional ethical approval was granted for the research to be conducted in Japan (National Institute of Public Health, Tokyo) and in the UK (Lancaster University Research Ethics Committee). Governance approvals were also gained from each hospital's Research and Development Department.

An active interview approach was adopted (Holstein and Gubrium 1995). The interviews focused on health professionals' decision-making relating to CBT, and their perceptions of the roles and responsibilities of others in the wider cord blood community. The transcribed data from the interviews were read multiple times and coded using Nvivo software. The codes were then grouped into over-arching themes and a thematic analysis was undertaken; the analysis was therefore an iterative process (Braun and Clarke 2006).

Results

Our data highlighted that understandings surrounding 'quality' within CBT can be divided into the following higher themes: product, expertise and collaboration, trust, and local experience and international accreditation. Epistemic uncertainty was present throughout the data.

Product

Participants declared the importance of cell dose and HLA match in CBU selection. However, participants challenged the certainty with which the importance of cell dose and HLA match has been presented in the cord blood community, and the priority given to one factor over the other in CBT.

> There are different views on the importance of two factors [cell dose and HLA match], which one is how important (Japan Consultant 2)

Regarding the acceptable minimum cell dose for successful CBT, participants highlighted the lack of certainty and scientific rigour in determining this number. Participants commented on differences between minimum cell doses, and the supporting research, used in the UK and Japan in particular.

> So there becomes a point, and there's a magic number that has been somewhat plucked out of mid-air of four and everybody uses this. Why do we use four? Well, because we've always used it. Where's your proof of it? (UK Transplant Nurse)

> Nobody knows what is the true lower limit [of viable cell dose] (Japan Consultant 1)

Whilst cell dose and HLA match were considered of importance by all participants, regardless of the associated epistemic uncertainty, they did not consistently agree whether other factors were associated with CBU 'quality' or not. CBU age and collection method were two such examples.

> But we do try to look for ones that are newer because they tend to be better quality (UK Consultant 2)

> We don't generally [consider the age of the cord as significant], no (UK Consultant 1)

Beyond these recognised factors, participants suggested there were many other potentially important factors that were not yet known to the cord blood community.

> There must be more factors other than HLA matching… However, these are still in a black box and yet to be understood. We believe these factors are valid, but not for sure (Japan Consultant 2)

Participants highlighted CBT research with contradictory outcomes conducted in Japan and the UK. Population differences between the two countries such as ethnicity were presented as justification for these differences, alongside the unknown yet important factors affecting CBT.

> There is inconsistency in evidence, we cannot explain it medically or scientifically…Because transplantation treatment is extremely complicated, a slightly different conduct, which may not look different, can often cause a completely different result (Japan Consultant 2)

These examples show how participants highlighted and generated uncertainty regarding

CBU product 'quality'. This created space for transplant centres and consultants to introduce their own experience and perspectives into the decision-making process.

Expertise and collaboration

Both UK and Japanese participants identified 'expert knowledge' as an important factor in determining CBU 'quality'. UK participants portrayed transplant consultants and tissue typers as 'the experts' within the CBT multidisciplinary team. Both expert groups acknowledged the importance of the other, which indirectly affirmed the significance of their own role within the team and allowed little space for others to gain authority. Transplant consultants from both countries displayed little knowledge of how CBUs were processed, for example they were unable to explain how bank laboratory staff processed a CBU following collection. This created a boundary between 'processing' and 'clinical' expertise in CBT, as well as the importance of collaborative knowledge.

> Yeah, that's kind of their job. That's what they do… ultimately I'm not going to be there going through and typing. I'm going to be a complete Luddite with it. I've got a patient, they need a transplant, provide me with something to transplant (UK Consultant 2)

> Then, if I was asked… how to collect samples or which method of storage is considered good, it would be difficult for me to give an answer (Japan Consultant 2)

Tissue typers were depicted by participants as providing 'scientific' expertise regarding the 'quality' of available CBU products in a supportive yet "*really integral*" (UK Consultant 1) role, which assisted the transplant consultants in their decision-making.

That tissue typers "*provide advice for other centres*" (UK Consultant 1) was perceived by participants as a sign of their excellence, and (international) collaboration demonstrated an individual's expertise. Yet, it also distanced the tissue typer from the 'core' transplant team. Transplant consultants were "*guided by what our tissue typing labs…tell us that is the best cord unit*" (UK Transplant Coordinator). To some extent, the transplant consultant presented their own expertise as limited in comparison to tissue typers. Yet, it also enabled the transplant consultants to present themselves as providing leadership, and having an ability to manage the complexity that arises within CBT; the complex decisions were therefore left "*mostly to the consultants and what they want*" (UK Transplant Coordinator). These portrayals set professional boundaries within the team; with knowledge forming around 'expert' and 'non-expert', 'scientific' and 'clinical', and 'core' and 'adjunct' team membership. By constructing differences between their roles in this way, transplant consultants and tissue typers cemented their own niche contributions within the team and prevented their role and expertise being encroached upon by the other. In this way, tissue typers were deemed as 'scientific' experts, whereas transplant consultants were 'non-scientific', patient-centred clinical leaders, with little overlap between the two. Equally, these divisions in knowledge mapped onto participants perceived "*territories of care"* with the laboratory as a territory whereby care was provided during the CBU during processing (Hardey et al. 2001). In contrast, the transplant centre was the site of care for the patient receiving the CBT.

British and Japanese participants presented decision-making as requiring the human oversight and experience of the transplant consultant, as they can "*make a comprehensive judgement, rather than focusing on one point*" (Japan Consultant 2). The desire to make one's own independent decisions, rather than rigidly following

guidelines, was presented as a 'natural response' by a UK Transplant Nurse, "*Nobody likes being told this is the only way to do it*". Japanese participants portrayed themselves as having greater trust in individuality in decision-making, and therefore were considered to benefit from greater clinical freedom and flexibility as a result. In turn, their British counterparts were depicted as restricted by the guidelines and policies of international organisations.

> If these people say it is 2 or 2.5 [cell count limit], even though they are in the countries of individualism…all the others say the same. Interestingly in Japan… it seems to me that they make a little allowance (Japan Consultant 1)

Japanese transplant consultants collaborated with individuals, although there was no mention of group or team discussion, as happened in UK selection meetings. In contrast, UK participants valued collaboration and regular communication with individuals within *"very small network(*s*)"* (UK Transplant Nurse), both locally and internationally. The perceived benefits were that collaboration promoted trust, improved relationships, and reduced uncertainty in decision-making. Additionally, the formation and protection of professional boundaries did not impede, but enabled collaboration between tissue typers and transplant consultants. They shared close relationships; trust and mutual respect built up over time as they adopted "*an open attitude*" (UK Consultant 1) towards each other.

Trust and uncertainty in the process

UK transplant consultants discussed their attempts to manage CBU uncertainty. They described the strategies they put in place to prepare for potential issues in order to

ensure overall CBT 'quality' e.g. assessing the viability of a thawed vial, double-checking HLA typing of the CBU itself once it arrived, and ordering back-up cords. These strategies were usually discussed with implicit or explicit reference to the consultants' inability to measure all the variables that could influence CBU processing. When patients had poor outcomes from their CBT, UK participants claimed they found it difficult to know where or when errors had occurred.

> Well, we've never quite sussed it out. It could have been from there or it could have been waiting around too long. It could have been the freezing process (UK Lab Manager)

These uncertainties mainly related to post-analytical issues, rather than analytical errors made by laboratory staff, and therefore highlighted the lack of quality indicators that transplant centres used to measure 'quality'. Conversely, UK teams felt vindicated in their strategies by positive CBT results. Put simply, the ends justified the means. The 'success' of a CBT was reinforced by the UK teams' portrayals of processing methods as difficult to change, and requiring validation, and team members required to adjust or learn new skills. The UK participants displayed less interest in methodological detail than their Japanese colleagues, who presented themselves as interested in the "*technical aspect*" (Japan Consultant 3) of CBU processing.

> So they need to find a better method and standardise if possible but at the end of the day the stuff that we're getting is actually okay so we're not hugely worried about it (UK Lab Manager)

Transplant consultants trusted CBU banks for different, but often related reasons. Trust was built through direct experience with a specific bank, the volume of and ease of access to information they received about a CBU, as well as a bank's reputation.

Japanese participants' trust in banks increased if they perceived 'quality' methods were used. This sense of trust was confirmed for Japanese participants when they checked the banks' methods, *"I do not believe anything until I check it by myself"* (Japan Consultant 3). In turn, Japanese participants developed trust for specific experts within a particular CBU bank, *"I think it is difficult unless you know people inside the institution"* (Japan Consultant 3). Essentially, people were deemed the most important quality indicator; hence, trust (in people) and quality were presented as synonymous. Positive experiences would encourage participants to use a bank again. In contrast, UK transplant centres had placed trust in international banks that they used based on the accreditation system, as it was impractical for them to visit every bank and assess its methods. This trust assumed a shared professionalism from all involved.

> The quality of what ends up being thawed after having been frozen, you have no idea. All you've got is a document that tells you what was put in the freezer… The handling of that unit when it's thawed out and washed by the stem cell laboratories, you're going to trust that they do it well and are competent to do it. There is… a lot of trust along the way with this (UK Tissue Typer)

Yet, UK participants undermined CBU selection when they claimed an inability to eradicate all uncertainties surrounding CBT. Once transplant centres had selected their 'most suitable' cord(s), UK participants expressed frustration that up to half of all patients would be affected by an unviable CBU having been selected and the delays that followed as a result.

> When you're presented with 100 units and a combination of any of those 100 units would fit the bill, the number of variations you're going to get is enormous. So there isn't necessarily an absolute right answer every time there

> can be two or three right answers (UK Tissue Typer)

For the UK participants then, uncertainty could not be removed from the CBU selection process, and instead was something that they accepted as part of the process.

Local experience and international accreditation

UK transplant consultants portrayed NetCord-FACT accreditation as the initial, yet essential, criteria that CBU banks must meet in order to gain a level of trust. Participants presented the accreditation as a pragmatic solution to assess the banks' methods of CBU collection, processing and storage. UK participants deemed CBUs from banks without accreditation to be inferior in 'quality' to those from banks with accreditation.

> It gives you that Kite mark, if you like. It's like if you go into the shop and you see something that's properly packaged and has Marks & Spencer written on it then there's a feeling that it's okay (UK Consultant 1)

However, a Japanese transplant consultant claimed NetCord-FACT standards *"cannot measure the technical aspect"* (Japan Consultant 3) of processing. For this participant these standards did not measure 'quality' per se. Even within accredited banks, it was considered that the 'quality' varied because of the range of different methods used. Not all accredited banks provided every piece of information mandated by the standards. Consequently, some UK participants claimed "*some [banks] are better than others"* (UK Consultant 2). All participants positioned the 'flexibility' within the standards arising from banks using different methods to claim accreditation as assuring 'safe processing' rather than 'quality'.

> The JACIE [NetCord-FACT] criteria are written so that they can be moved a little bit. It's not you must absolutely do this, this and this it's a guideline to say these are the things we expect you to do. Can you prove that you do these things in the right way to give you the right result at the end? (UK Transplant Nurse)

Both UK and Japanese participants prioritised banks with which they had previously used and the experience had been positive. Yet, it was "*the quality of [a] person's experience* [and] *the degree of experience*" (Japan Consultant 1), including both failures and successes, that influenced and informed participants' trust in a bank. One Japanese participant suggested that experience could compensate for cell doses lower than the acknowledged lower limit to ensure outcomes perceived as 'quality' CBT.

Both UK and Japanese participants displayed preferences in the banks from which they received CBUs, although their preferences were not based on evidence available in published literature or international guidance. Japanese centres were depicted by participants as having a preference for CBUs from domestic banks because international transportation was perceived as increasing the risk of accidents, "*Japanese banks are more familiar and their regulations are known*" (Japan Consultant 2). Equally, with CBUs from abroad, "*there are unknown elements there*" (Japan Consultant 2). By comparison, UK transplant centres chose domestic CBUs for their lower associated costs.

Japanese transplant consultants' preferences were described as "*spontaneously formed… not a policy*" (Japan Consultant 2) and based on their own local experiences.

> In reality, we have [preferences amongst CBU banks]. Officially, we, like others, do not have any preference (Japan Consultant 2)

Japanese participants claimed that over time their CBU selection preferences developed to form an internal "*house rule(s)*" (Japan Consultant 2) at each transplant centre. This implied an important role for tacit knowledge in CBU decision-making. UK participants also discussed the influential role of tacit knowledge in their decision-making. The introduction of a centralised 'centre of excellence' model for CBT to be conducted in the UK was mooted during interviews, with UK participants expressing concern that local knowledge would "*probably wither on the vine*" (UK Consultant 1) if implemented. Knowledge acquired through local experience therefore was implied to be a valued resource for those working in transplants centres and a tool to draw upon when faced with uncertainty around 'quality' CBU.

Discussion

The international CBT community is known to exist as a complex bionetwork, with overlapping roles played by different stakeholders, and individual countries having varied positions within the network. However, understanding of the CBT bionetwork has tended to focus on research settings, rather than clinical settings (Sleeboom-Faulkner and Patra 2011). Our findings therefore extend understanding of the CBT bionetwork by focusing on the perspectives of and relationships between different stakeholders, including transplant centres and tissue typers (See Table 2).

In our study, Japanese transplant consultants did not discuss local collaboration in the way UK participants did. Instead, Japanese participants highlighted the importance of generally having trust in individuals performing key tasks (including CBU processing). UK consultants displayed greater faith in the knowledge of others than their Japanese colleagues, who required a personal experience of an individual to develop trust. The trust of Japanese transplant consultants was built on a one-to-one and

direct basis, with more pre-requisites and not extended to organisations or groups of individuals (particularly on an international level). This distrust of international organisations may be a consequence of previously failed projects in Japan (e.g. Protein 3000 Project), where political interference significantly contributed to project failure (Fukushima 2016; Sleeboom-Faulkner 2011). Furthermore, our Japanese participants' more individualistic approach is likely to be informed by the country's CBU self-reliance, whereas UK consultants actively engaged with international colleagues and valued international policies (e.g. NetCord-FACT standards, national guidelines), and their resulting positions in the bionetwork as identified by others (All Party Parliamentary Group on Stem Cell Transplantation 2012; Brown and Williams 2015; Titmuss 1970; Williams 2015). ().

On CBT 'quality', transplant consultants from both countries highlighted the importance of trust in colleagues, in processing, and in information, as well as in collaboration. Our participants from UK centres set clear professional boundaries between 'experts' (tissue typers and transplant consultants), which were portrayed as central to successful local collaboration. Both sets of experts were secure with these boundaries as it permitted meaningful collaboration to occur, resulting in these boundaries being transcended (D'Amour et al. 2009; Freeth 2009). The strength of the transplant consultant-tissue typer relationship was presented by UK participants as key to the 'quality' of local decision-making. Tissue typers were trusted by transplant consultants with the 'science' of CBU selection as their area of expertise. However, leadership of the selection meeting and wider MDT relied on the knowledge of clinical factors (e.g. transplant urgency), so could only be provided by transplant consultants; this leadership was uncontested. So, whilst 'scientific' roles have been portrayed as superior and holding authority (Gieryn 1983), transplant consultants downplayed any

scientific aspects to their role. They comfortably presented tissue typers as 'scientific' experts, which maintained professional boundaries and cemented their own role as clinical leader. In turn, the clinical setting was subtly presented as of equal standing to the 'scientific' laboratory domain. This is in keeping with the interplay witnessed between counsellors, scientists, and embryologists and the constructed boundaries of expertise surrounding the 'clinical' and 'scientific' in the context of embryo donation for stem cell research (Machin and Williams, 2017).

Whilst NetCord-FACT accreditation is valued highly within CBU banks and provides some standardisation between banks, our study participants suggested that the standards were imperfect, with variable compliance by CBU banks to every requirement set out in the standards. The difference in the value attributed to NetCord-FACT accreditation by those in transplant centres and in CBU banks reinforces the importance of perspective and position within the bionetwork, and highlights the discursive nature of CBT 'quality'. CBU banks have independent control of their processing methods, within the broad boundaries of NetCord-FACT standards (Brown, Machin and McLeod 2011), whilst transplant centres hold minimal power over processing CBUs. Our findings therefore highlight one of the many felt vulnerabilities by transplant centres in the context of cord blood quality. Accreditation was used by participants in the transplant centres as a proxy for trust in CBU banks' methods, as it assumed a degree of professionalism from CBU banks, until transplant centres have developed sufficient experience and trust with a bank. This further highlights the importance of trust and experience within CBT 'quality', as well as how 'quality' is interpreted differently depending on one's position within the bionetwork. Thus, trust was used as by participants from both countries as a measure of 'quality' within CBT decision-making.

Epistemic uncertainty was accepted by transplant consultants from Japan and the

UK as an unavoidable part of CBT, and even generated by them during interviews. The presentation of 'definitive' limits within selection guidelines, such as the minimum acceptable cell doses, contradicts this uncertainty and ignores the existence of the "*black box"* factors described by our participants in transplant centres. This is exacerbated by the variation between different country's guidelines and frequent changes to guidelines (Barker et al. 2011; Dehn et al. 2019; Hough et al. 2016; Politikos et al. 2020; Rich 2015, Shaw et al. 2009). When defining 'quality' in CBT, selection guidelines assume a level of detailed information from the banks that our participants claimed was not always provided. Guidelines cannot account for nuance in individual patient factors or clinicians' personal preferences. By generating and affirming epistemic uncertainty, transplant consultants created space for themselves to exercise clinical autonomy and justified using their own experiences rather than available data and literature alone. Transplant consultants attempted to 'own' the epistemic uncertainty of CBT by accepting responsibility for decision-making from their colleagues and the risks that are associated with decision-making. In doing so, they acquired the trust of their colleagues, reduced uncertainty within the team, and retained clinical autonomy.

Guidelines cannot support consultants' decision-making when pragmatism is required, as it so often is in clinical practice with uncertainty. For example, what should transplant centres do when multiple (or no) CBUs meet the requirements of the selection criteria? Instead, transplant consultants make collaborative and pragmatic decisions informed by prior experience. This creates a constantly changing and adapting model for decision-making. Our study affirms the existence of a CBT bionetwork, made up of *"rapidly changing landscapes"*; hence, this adaptive, experience-based decision-making model is more appropriate than fixed selection criteria (Sleeboom-Faulkner and Patra 2011; Williams 2018). The unwritten "*house rule(s)"* of local tacit knowledge

augment official policies and are exerted within the boundaries of selection guidelines. Application of experience and local tacit knowledge ensures that decision-making works effectively in the real world; it helps transplant consultants to manage epistemic uncertainty when making decisions, where guidelines cannot. The sum value of local tacit knowledge arguably exceeds the sum of the individuals forming each team, and therefore should be valued when planning national services in the future. Transplant centres should continue sharing best practice based on their experience and to safely push the boundaries provided by current guidance.

This paper broadens our understandings of CBT 'quality', looking beyond CBU 'quality' alone. We have explored perspectives from UK and Japanese transplant centres, as *"regime(s) of truth"* on current clinical practice (Martin, Brown, and Turner 2008; Moreira and Palladino 2005; Williams 2015), and what 'quality' means to their staff in practice. Whilst guidelines take a quantitative approach and scientific focus to 'quality' (Hough et al. 2016; Politikos et al. 2020), little attention has been paid to the role of qualitative factors influencing and informing CBT 'quality' for those working in clinical practice. We support Querol et al's (2010) call for a shift in focus from 'quantity' to 'quality' in CBUs and argue for further qualitative research to advance understandings surrounding CBT 'quality'. Trust, collaboration, (un)certainty, expertise and experience are some of the key components that have been identified in our study as influential on understanding 'quality'. Given the main limitation of this study was the small sample size, we anticipate that different transplant centres and stakeholders may hold varying perspectives of CBT 'quality' in addition to those we have identified in our study. Further large-scale qualitative research is needed to explore these identified concepts involving transplant centre teams and to delve deeper into the qualitative aspects of CBT 'quality'.

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Table 1: Examples of uncertainties surrounding key 'quality' markers for CBU based on published literature

CD34+ count	CD34+ count has been criticised as a poor marker of stem cell presence as many CD34+ cells do not play a role in engraftment (Rich 2015).
CD34+ count and HLA match	Higher CD34+ count and closer HLA-match have been shown to correlate with improved survival (Wagner et al 2002, Eapen et al 2011).
CD34+ and viability	CD34+ viability is more closely associated with successful engraftment than CD34+ count (Scaradavou et al. 2010). There is high variability between laboratories calculating CD34+ count and measuring cell viability, including CD34+ viability, "*remain(s) difficult*" (Hough et al. 2016).
TNC count and CD34+ count	TNC count can be used as a surrogate for CD34+ count and is comparatively easy for laboratories to measure. A retrospective evaluation has shown no clinical differences when using TNC count alone, rather than together with CD34+ count, in CBU selection (Jaime-Pérez et al 2011). This only shows that TNC count can provide good clinical outcomes, not that it is a good marker of CBU 'quality'. High TNC and CD34+ counts do not measure stem cell potency (i.e. dose required for successful engraftment), which has been argued to be a more accurate measure of 'quality'.
TNC counts and potency assays	To improve understanding of CBU 'quality', some suggest that banks should be performing potency assays to know a CBU's biological activity and testing the thawed unit rather than the pre-frozen one (Rich 2015). By using TNC counts that achieve

	good clinical outcomes, UK guidelines display an inclusive, pragmatic definition of CBU 'quality', rather than stringently relying on potency (Hough et al. 2016).

Table 2: A comparison of UK and Japanese consultants' decision making when contemplating 'quality' cord blood units

UK Consultants	Japanese Consultants
Trust formed through local collaboration	Trust in individuals in performing key tasks
Trust created through knowledge of others in the process and system	Trust created through past experiences of working with individuals in the process and system
Trust in organisations and in teams	Trust on a one-to-one basis, and direct experience with individuals
Trust working within international policies	Trust generated by setting more pre-requisites to determine 'quality'
Country reliant on international network	Country self-reliant

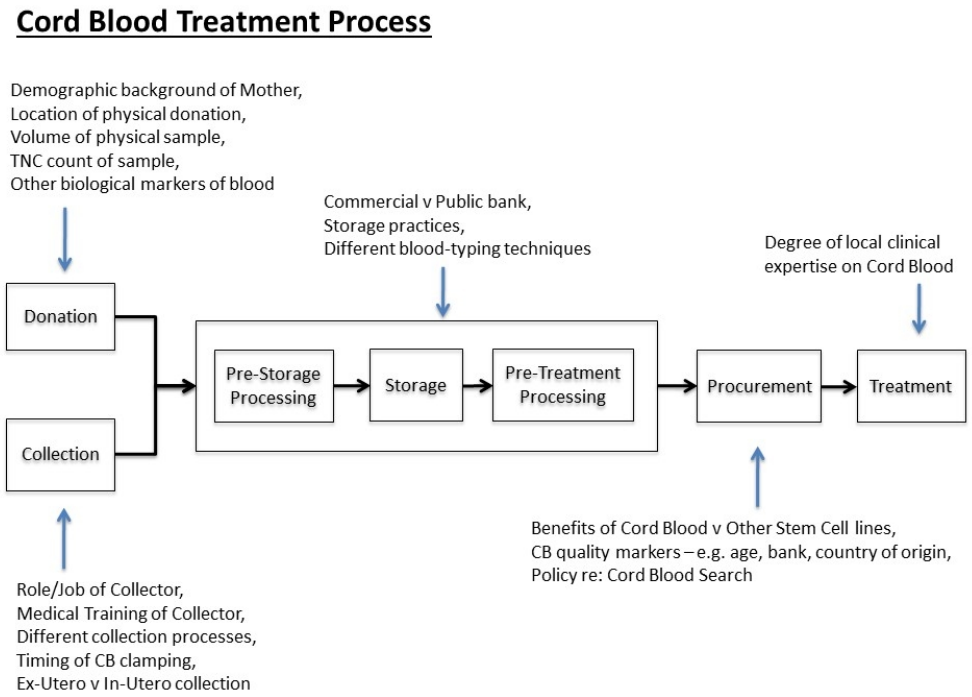

Figure 1: Cord Blood Treatment Process. The Cord Blood Treatment Process that was developed following interviews. A number of factors that contribute to the 'systems' uncertainty have been noted for each phase of the process.

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