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### Citation for published version:

Hopkins, C, Sydes, M, Murray, G, Woolfall, K, Clarke, M, Williamson, P & Tudur Smith, C 2015, 'UK publicly-funded Clinical Trials Units supported a controlled access approach to share individual participant data but highlighted concerns', *Journal of Clinical Epidemiology*.  
<https://doi.org/10.1016/j.jclinepi.2015.07.002>

### Digital Object Identifier (DOI):

[10.1016/j.jclinepi.2015.07.002](https://doi.org/10.1016/j.jclinepi.2015.07.002)

### Link:

[Link to publication record in Edinburgh Research Explorer](#)

### Document Version:

Peer reviewed version

### Published In:

Journal of Clinical Epidemiology

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# Accepted Manuscript

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PII: S0895-4356(15)00339-X

DOI: [10.1016/j.jclinepi.2015.07.002](https://doi.org/10.1016/j.jclinepi.2015.07.002)

Reference: JCE 8943

To appear in: *Journal of Clinical Epidemiology*

Received Date: 3 February 2015

Revised Date: 22 May 2015

Accepted Date: 6 July 2015

Please cite this article as: Hopkins C, Sydes M, Murray G, Woolfall K, Clarke M, Williamson P, Tudur Smith C, UK publicly-funded Clinical Trials Units supported a controlled access approach to share individual participant data but highlighted concerns, *Journal of Clinical Epidemiology* (2015), doi: 10.1016/j.jclinepi.2015.07.002.

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**individual participant data but highlighted concerns**

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**Objective:** Evaluate current data sharing activities of UK publicly funded Clinical Trials Units (CTUs) and identify good practices and barriers.

**Study Design and Setting:** Web based survey of Directors of 45 UK Clinical Research Collaboration (UKCRC) registered CTUs.

**Results:** 23 (51%) CTUs responded: Five (22%) of these had an established data sharing policy and 8 (35%) specifically requested consent to use patient data beyond the scope of the original trial. 15 (65%) CTUs had received requests for data and seven (30%) had made external requests for data in the previous 12 months. CTUs supported the need for increased data sharing activities although concerns were raised about patient identification, misuse of data, and financial burden. Custodianship of clinical trial data and requirements for a CTU to align its policy to their parent institutes were also raised. No CTUs supported the use of an open access model for data sharing.

**Conclusion:** There is support within the publicly funded UKCRC registered CTUs for data sharing but many perceived barriers remain. CTUs are currently using a variety of approaches and procedures for sharing data. This survey has informed further work, including development of guidance for publicly funded CTUs, to promote good practice and facilitate data sharing.

**Key words:** Data sharing; Individual Participant Data; IPD; Clinical trial; Publicly-funded; Clinical trials unit

**Running title:** Clinical trial data sharing in publicly-funded Clinical Trials Units

**Word count:** 4,312

## 1 INTRODUCTION

Historically, many researchers have considered data generated in the conduct of a clinical trial as “private property” belonging to the trial sponsor or original research group (1). As a result further use of the data has often been restricted to those researchers, possibly limiting the research potential of valuable data. Progress is being made and the potential added value of sharing clinical trial data is becoming more widely accepted. In particular, the sharing of patient level data could enhance many research-related activities (2, 3). Secondary analyses and meta-analysis of Individual Participant Data (IPD) could reveal directions for future research and reduce the requirement for further clinical trials, and therapies could be made available to patients more quickly (4, 5).

The incentives for sharing clinical trial data in conjunction with concerns of publication bias and selective reporting practices have led to significant growth in support for initiatives that could lead to greater trial transparency, aiming to promote open science, benefit the public’s health, and reduce wasteful research (6-10). Recently, focus on sharing data from clinical trials has led to consideration of how industry, regulatory bodies and clinical trial funders can amend their practices to facilitate clinical trial transparency. The AllTrials campaign (11), calls for all past and present clinical trials to be registered and their full methods and summary results reported, and has the support of representatives from regulatory bodies, industry, publishing groups, research funders and many others. The European Medicines Agency (EMA) has recently released a policy for “Publication and access to clinical-trial data” (12), and the Association of the British Pharmaceutical Industry (ABPI), the Institute of Medicine (IOM), and the European Forum for Good Clinical Practice (GCP) are among many groups to have held workshops discussing sharing clinical trial data and ensuring transparency (13-15). The British Medical Journal (BMJ) strongly supports transparency and data sharing with a policy stating that “from Jan 2013 trials of drugs and medical devices will be considered for publication only if the authors commit to making the relevant anonymised patient level data available on reasonable request” (16). Significant steps towards transparency are being made by some pharmaceutical companies. The collaborative website <https://www.clinicalstudydatarequest.com/> provides a route to request access to anonymised patient level data and supporting documents from multiple sponsors (17, 18). Separately, the Johnson & Johnson agreement with the Yale University Open Data Access (YODA) project allows third party access to their data (19).

Much of the publicity surrounding the topic of clinical trial data transparency has featured stakeholders involved with commercially funded clinical trials. However, clinical trials are also designed, coordinated, analysed and reported by

publicly funded sponsors. Indeed 58% of intervention trials registered in clinicaltrials.gov (October 2014) have non-industry sponsors, and they too have a duty to consider procedures to make patient level data available. Rathi et al (20) surveyed 317 trialists from a range of sectors to evaluate levels of support and concerns associated with clinical trial data sharing and the Cochrane IPD Meta-analysis Methods Group were surveyed in 2011 (21). Both surveys demonstrated that public sector researchers are generally in support of making clinical trial data available. This is further evidenced by several examples of publicly funded clinical trialists making data available through open access systems (e.g. VISTA, ADNI, NIDDK) (22-24), by providing IPD for meta-analysis (e.g. ACCENT database, INDANA) (25, 26) and as part of wider genetic data consortia (e.g. Biomarkers Consortium, PRO-ACT) (27, 28). Despite this progress, accessing clinical trial data from publicly funded clinical trials can sometimes be difficult, if not impossible, and further steps are needed to encourage and facilitate future sharing.

The UK Clinical Research Collaboration (UKCRC) Registered Clinical Trial Unit (CTU) network includes 45 publicly funded Clinical Trial Units that design, conduct, analyse and publish clinical trials across different diseases and settings. The CTUs are notable in that they can be involved in both sides of data sharing; requests for data are made to the units from external researchers, and members within the units can also be involved in requesting data from other sources. The CTUs are a potential vehicle to facilitate data sharing of publicly funded trials in the UK and could provide a model of good practice for other publicly funded trials. Therefore, we surveyed CTU directors to capture current practice, identify perceived barriers and explore attitudes to help inform the development of guidance to facilitate data sharing of publicly funded trials.

## **2 METHODS**

### **2.1 Survey instrument development**

We developed a 47-item questionnaire as part of an MRC-funded project. Questions were selected by the research team using their expertise and experiences of data sharing activities. The survey was developed and conducted online using SelectSurvey.NET. The complete survey is provided as supplementary material. A brief synopsis and link to the survey was emailed to the UKCRC-registered CTU Directors in April 2014. Email reminders were sent after 2, 4 and 6 weeks. Multiple responses from the same unit were combined where complementary; otherwise the response of the most senior CTU member was used.

The questionnaire took approximately 15 minutes to complete. Ethical approval was obtained from the University of Liverpool Research Ethics Committee. As the survey was conducted online, completion was regarded as consent to participate.

## 2.2 Survey domains

Multiple choice, Likert scale and free-text questions covered the areas of:

- i. Current practice
- ii. Custodian experience
- iii. Requester experience
- iv. Future perspective
- v. Standards and awareness
- vi. Models for data sharing
- vii. Requirements and potential problems

## 2.3 Response analysis

Free text responses were reviewed and categorized by two of the research team (CH and CTS) with categorizations compared and agreed. Results were summarized using descriptive statistics.

## 3 RESULTS

There were 24 responses from 23 (51%) registered CTUs across the UK (two responses were received from the same CTU). Three of the responders provided partial information and have therefore only been included in relevant sections of the results. From 24 responses, the majority (71%) were completed by the CTU Director or Deputy Director with seven (29%) completed by delegated members of the CTUs including statisticians, operations managers, data managers and trial managers. Responding CTUs conducted trials in many diseases, all trial phases, and included clinical trials of investigational medicinal products (CTIMPs) and non-CTIMP trials; there were no specific trial phases, disease types, or methodological research areas that were under-represented in the survey compared to non-responding CTUs.

Five of the 23 CTUs (22%) had an established Data Sharing Policy, 11 (48%) had a policy in development, but seven (30%) had no immediate intention of developing a policy.

Eight (35%) CTUs indicated that consent is generally sought from participants in clinical trials for their data to be used outside the original scope of trials (Figure 1). However, a standard phrase was not being used across the CTUs. Examples of text used include: “agree to allow any information or results arising from this study to be used for healthcare and/or further medical research upon the understanding that my identity will remain anonymous wherever possible”; consent for “medical data to be collected for this study and may be used to develop new research and that data protection regulations will be observed”; “used for future research and to be transferred to research institutes within the UK”; consent for separate blood samples to be “anonymized and stored for infection and immunity-related research in the future”; consent for “participants to be contacted independently by other researchers to take part in research within the same disease area”.

#### **Figure 1: Current practice regarding data sharing policy and consent from participants to share their data**

Of the 15 (65%) CTUs that do not currently specifically request consent for patient data to be used beyond the scope of the original trial, 12 (80%) would be prepared to request broader consent in the future (one only if the CTU signed up to a central repository in future) but two (13%) would not, giving the following reasons; “This should not be CTU policy – needs discussion and approval of other parties” and “This should be a condition of ethical approval or funding – the CTU only handles data on a subset of studies and this is a much wider issue”. One CTU did not provide a response.

#### **3.2 CTU experience of sharing data**

15 (65%) CTUs had received at least one request for data in the previous 12 months. Most commonly, two requests had been received but four CTUs had received at least five data requests. Institutes of higher education were the most common requester of data (n=10), followed by NHS Trust/Clinician (n=6), Independent Researcher (n=5) and Industry (n=4). The most common reason for requesting data was for meta-analysis. No recent requests had been refused, although some were only partially fulfilled due to conflict with other research projects or pre-planned analyses within the CTU. Patient consent, quality and originality of research proposal, verification of governance, timing of request and labour intensity of fulfilling the request were the most common considerations (reported by at least two thirds of the

CTUs) when reviewing requests for data from the CTU (Figure 2). There were no reported issues with providing the data in the format that had been requested.

**Figure 2: Considerations when reviewing requests for data as reported by 15 CTUs that had received a request in the past 12 months**

14 (93%) of the 15 CTUs that received requests had also received a research proposal outlining the purpose of the data request for at least one request, but only nine (60%) CTUs utilised a data sharing agreement. Six (40%) CTUs received 'Requester credentials to signify competence to analyse data', and five (33%) had received 'assurances that there would be no attempts to retrospectively identify patients' as part of their data sharing process.

CTUs that had been involved with sharing data were asked about the resources required and whether certain activities were more difficult for older trials (>5 years old) compared to more recent trials. The majority (93%) stated that the location and preparation of the data was resource intensive (defined in our survey as more than half a day to complete) and this was the most frequently cited activity (n=6, 40%) felt to be more difficult for older trials compared to more recently completed trials. Ten (67%) CTUs described the anonymisation of data as 'not likely to be resource intensive' and only two (13%) felt that this would be more difficult for older trials. Reviewing requests for validity was considered more difficult by three (20%) CTUs, and two (13%) described generating data sharing agreements as more difficult for historical data.

### **3.3 CTU experiences of requesting external data**

Of all 23 responding CTUs, seven (30%) had made an external request for data in the last 12 months. Six of these provided additional information about the external requests; four CTUs (67%) had made two requests, and two CTUs (33%) had made more than five requests. These requests had been made to: 'Institute of higher education' (n=3), 'Industry' (n=2), 'NHS Trust/Clinician' (n=2), 'Independent researcher' (n=2), and 'Other' ("NHS Data – Information Centre" (n=1) and "Health and Social Care Information Centre" (n=1)). All six CTUs had made successful requests and data had been provided either completely (n=4, 67%) or partially (n=2, 33%). There was considerable variation in the time taken between their initial request and the provision of data ranging from a few weeks to over a year. Reasons given for making the data requests were provided by the six CTUs as: meta-analysis (n=4), follow up of trial participants (n=2), methodological research (n=1), and feasibility of setting up registry (n=1). All six CTUs had been required to

submit a research proposal and data sharing agreement and some were required to provide assurances they would not attempt to retrospectively identify patients (n=3) and provide credentials or proof of competency to analyse the data being requested (n=2).

### 3.4 Future Perspectives

#### 3.4.1 Standards and Awareness

21 CTUs rated their knowledge of various data sharing initiatives, policies and incentives. The AllTrials campaign was the most well-known, with 13 (65%) responders indicating they had 'excellent' or 'good' knowledge of the campaign (1 non response). The YODA (Yale Open Data Access) initiative was least well known with 18 (86%) 'unaware' of the project. Responders had some awareness of the draft EMA Policy, clinicalstudydatarequest.com website, the BMJ policy on data sharing and data sharing policies of clinical trial funders (Figure 3). Examples of other initiatives or policies that respondents were aware of included the "new EU Clinical Trial regulation", "NHS Information Governance and the NHS Consortium", "US Institute of Medicine", "PLOS" and "NIH" policies.

#### **Figure 3:** Awareness of various data sharing initiatives and policies

As the use of common data standards across trials could simplify data sharing, the CTUs were asked if there were any data standards commonly used within the unit. 11/21 (52%) CTUs stated that they apply standard formats for their electronic data. MedDRA (Medical Dictionary for Regulatory Activities) was the most frequently named standard (n=6), but CDISC (Clinical Data Interchange Standards Consortium) (n=2), and CTCAE (Common Terminology Criteria for Adverse Events) v4.0 (n=1) were also mentioned.

12/21 CTUs (57%) would be prepared to adopt a standard data sharing policy (standardised for the UK CRC CTUs as a minimum), but nine (43%) indicated that there were specific reasons or external influences that would prevent their CTU adopting a standard data sharing policy – these were categorised as; process cannot be standardised; standardising data too complicated; overarching university and NHS policy on data sharing; variety of governance structures for different data types; conditions to involve the trial team in review of data request and include trial investigator on publication; burden on original researchers; patent/IP issues; ownership of data; misuse/incorrect secondary analysis; participant consent; ethical approval; logistical and cost implications. 14/20 (70%) CTUs would be prepared, in principle,

to transfer data to a central repository assuming it was legal and ethical. Many used a free-text box to indicate associated concerns about confidentiality, funding and the issue of data ownership.

### 3.4.2 Models for data sharing

An 'internal review' model, in which the data custodian would review and assess a request based on criteria such as scientific soundness of the proposal or competence of the requestor to perform the specific proposed analyses, was considered the most suitable model for granting access to data (n=15/20, 75%). Five (25%) CTUs preferred a 'learned intermediary' model with requests for data reviewed independently by a review panel. Notably, none of the CTUs considered an 'open access' model with no required approval process as 'most suitable' (Figure 4). CTUs commonly considered (n=9/19, 47%) access through 'restricted interface' model as most suitable for data provision; the data custodian maintains possession but grants access to an external requestor through a specific secure interface with restrictions on data download. Five (26%) supported an approach whereby data would be uploaded to and downloaded from a central independent repository, and an equal number (n=5, 26%) viewed 'direct transfer' of data to external parties without a repository as most suitable (Figure 4). One responder included a further suggestion for "Controlled access with active engagement from trial team as research partners".

#### Figure 4: Models rated "Most suitable" by responding CTU

21 CTUs provided opinion about the most appropriate time for making data available at the end of a trial; 10 (48%) CTUs selected 'At any time after the trial team have completed all analyses and secondary exploratory analyses'; 1 (5%) selected 'As soon as final analysis is complete'; 2 (10%) chose 'within 12 months of last patient last visit'; 1 (5%) chose 'within 24 months of last patient last visit'; 6 (29%) CTUs provided free text responses categorized as: timing would vary by trial (2); after the trial results have been published (4). One (5%) provided a data sharing policy which suggested a period of exclusivity determined on a per trial basis (generally a minimum of five years from last patient last visit).

### 3.4.3 Potential Problems

20 CTUs provided at least one response to a Likert scale question (Figure 5) addressing levels of concern on specific topics. The risk of incorrect secondary analyses and misuse of data was of greatest concern with all but one CTU stating they were moderately (n=7/20, 35%) or very concerned (n=12/20, 60%), and most CTUs were moderately (n=6/18,

33%) or very concerned (n=8/18, 44%) about the resource implications of sharing data. CTUs were fairly evenly split across being very (n=7/20, 35%), moderately (n=6/20, 30%), or not very concerned (n=7/20, 35%) about the loss of IP/ability to publish. The 'Identification of patients' and 'additional consent requirements' split the CTU opinion with approximately half being "very" or "moderately" concerned and the other half "not very" or "not at all" concerned. Some "Other" concerns were raised by three CTUs, specifically the qualifications of applicants to analyse data, repository security, patent protection, and potential impact on future trial recruitment.

**Figure 5:** Level of concern about frequently raised barriers to making full clinical trial data available on a controlled access platform

CTUs were asked to indicate problems foreseen if all data (including IPD) were to be published on a controlled access platform. 11/23 (48%) CTUs raised concerns about time and resource implications of making datasets available (n=6), getting all CTUs on board with a central repository or standard data formats (n=4), how to deal with subsets of patients withdrawing consent or not providing it in the first place (n=3), the right of the sponsors or investigators to maintain rights over the use of the data and to be acknowledged appropriately where data are shared (n=4), and the risks of "bad research" both to the original research group and patients (n=3).

#### 4 DISCUSSION

This survey explores the data sharing views and experiences of publicly funded CTUs in the UK. The media attention that has surrounded the issue of clinical trial data sharing within the last few years has mostly focused on clinical trials of investigational medicinal products (CTIMPs) conducted within the pharmaceutical industry, but most of the issues, and the need to share data, apply equally to publicly funded clinical trials. The CTUs that responded to this survey are fundamentally different to the pharmaceutical industry. They are involved in a diverse range of trials including CTIMPs, device trials, surgical trials, pragmatic trials and observational studies. They do not set out to make a profit from the sale of the interventions being investigated and trials within their portfolio are typically funded by public or charitable organisations. This often creates complex sponsorship arrangements that may introduce a level of ambiguity about ownership and responsibilities for sharing the data generated in the clinical trial. Publicly funded CTUs may also be linked to, or be part of, parent organisations such as Universities or NHS Trusts, and they may also conduct clinical trials in collaboration with industry, hence may need to consider these overarching data sharing requirements in addition to those of the CTU, the funder, potential journal, and any relevant regulatory requirements. We would therefore strongly

recommend that the issue of data sharing is explicitly and thoroughly discussed between stakeholders during the planning of a publicly funded trial to agree roles and responsibilities. Indeed, we fully support the recommendation in the SPIRIT 2013 checklist that a dissemination policy should be described in the trial protocol, with specific reference to “Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code” (29).

Our survey showed a variety of attitudes towards data sharing and different levels of activity and knowledge about current data sharing initiatives. CTUs may not yet have developed their procedures for sharing data due to a low demand and inadequate resources. However, if CTUs were to take a more proactive role in sharing data, awareness of the wealth and potential value of the data that are available could be increased. Of course this would have a resource implication which is a common concern and potential barrier for publicly funded CTUs. Funds may be provided to a sponsor to facilitate data sharing in future trials, but historically there has been no provision to cover costs of wider data dissemination. Trialists now need to plan ahead for this and include appropriate costs for data set preparation and sharing in the same way as may be done for open access publication or archiving trial data.

Consent from patients to share anonymised data is often viewed as a prerequisite for data sharing and one simple approach to remove this perceived barrier for future trials would be to actively seek consent from patients for this purpose. Our survey suggests that only a minority of publicly funded CTUs currently request consent for sharing data in their trials, yet most CTUs were supportive of a move towards such an approach. Furthermore, it is worth mentioning that even if explicit consent to share anonymised data has not been requested from patients in ongoing or completed trials, this does not preclude the sharing of anonymised data; the Data Protection Act no longer applies to data from deceased participants or data anonymised such that the individual is no longer identifiable (30). As an example of this, the International Stroke Trial Collaborative Group has made the data from their publicly funded clinical trial publicly available (22). They note that “Consent for publication of raw data was not obtained from participants” and since “the dataset is fully anonymous” they present the view that “publication of the dataset clearly presents no material risk to confidentiality of study participants”.

Those CTUs that had been approached for data in the last 12 months had provided data in all instances, albeit using different, possibly ad-hoc, approaches. Adoption of a standard procedure, or at least some common principles across the CTUs, would greatly facilitate data sharing. The concept of a clinical trial data repository that CTUs could transfer data to was met positively, though there were differing opinions about the format this repository should take

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demonstrating the difficulty of a “one size fits all” approach. Nevertheless not one CTU felt that an open access approach would be appropriate; the risks of bad research resulting from poor secondary analyses or incorrect replication of primary analyses, and risks of patient identification, could be mitigated through a controlled access system with data requests supported by evidence of the research team’s expertise and a research plan providing details of proposed analyses. This practice has already been adopted by some CTUs and requesting this information or having to provide it does not seem to present a barrier to sharing activities. Furthermore, ensuring that the data sets are fully annotated and accompanied by all associated trial documentation such as the protocol and blank Case Report Forms (CRFs) should further minimise the possibility of conflicting results arising from replicated analyses. If reanalysis of the same data did produce conflicting results then this should firstly be discussed with the original team, and if discrepancies remain, this information should of course be made publicly available.

Sharing IPD from clinical trials is only one part of a wider move towards ‘open science’ that promotes open access to journal articles, protocols, source code, and data. Some may criticize an approach of sharing IPD with researchers within a controlled system as not being ‘open’ enough and may advocate data being openly available for all to access without restriction. The clinical trials community must ensure that all reasonable precautions are taken to protect the privacy and confidentiality of trial participants and this should always be the overriding consideration. Taking unnecessary risks could lead to more harm than good and we support the use of a controlled access approach as discussed by Sydes et al (31) .

#### *Limitations of study*

This survey was limited to UKCRC-Registered CTUs and may not necessarily be representative of all UK CTUs or organisations that conduct publicly funded trials. It was targeted at CTU Directors but was completed by delegates in some cases. As the survey addressed current practices within the CTUs there should not have been any impact of the responses being provided by someone other than the Director. However, it is possible that responses represent a partly political view rather than the personal opinion of scientists. The survey was short and simple but only 51% of invitees provided useable responses; this level of response is typical of web-based surveys (20, 32). Reminders were sent regularly by email but more responses might have been received had follow up occurred via telephone or if the survey remained open for longer. We feel that the responses provide a good representation of the UK stakeholder group; there was no clear under-representation of any particular subset of CTUs as a wide spread of phases, trial types, disease areas, and unit sizes were represented amongst the responding CTUs. Open questions allowing free text answers

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enabled responders to present additional issues, concerns and suggestions that may have been shared by other responders had they been presented as options within the original survey. Our threshold for defining 'resource-intensive' one half-day (i.e., 4 hours) was too low.

#### *Future directions*

The information gathered indicates that there is general support for clinical trial data sharing within these publicly funded CTUs, but there are several perceived barriers that may be preventing initiatives from moving forward. This information has been used to inform the development of good practice guidance for publicly funded CTUs to encourage future data sharing (33).

#### *Conclusions*

Sharing clinical trial data is at the forefront of many discussions by regulatory bodies, research funders and the pharmaceutical industry with an aim to increase transparency and facilitate efficiency and advances in research. Publicly funded CTUs have an important role to play in this arena. The wealth of experience and knowledge within the units could help establish an infrastructure to facilitate data sharing and improve the use of publicly funded clinical trial data for the public good. Action is now needed to focus efforts towards facilitating further clinical trial data sharing and developing good practice for data sharing in publicly funded CTUs.

## **5 ACKNOWLEDGEMENTS**

We would like to thank all the participants in this survey for their valuable input and the following for helpful comments during the development of the survey; Liz Tremain, Paul Mason, Gill Booth, Jan Bogaerts, Richard Riley, and Jane Armitage. We would like to thank the MRC Network of Hubs for Trials Methodology Research for funding this work.

## **6 AUTHOR CONTRIBUTIONS**

CH designed the survey, monitored data collection for the survey, analysed the responses and drafted and revised the manuscript. CTS initiated the collaborative project, designed the survey, analysed data and revised the manuscript. PW, MS, KW, MC and GM all contributed to the design of the survey and revised the manuscript. Review and revision was provided by all authors. CH and CTS had full access to all of the data and can take responsibility for the integrity of the data. CTS is guarantor. All authors approved the final version of the manuscript.

**FUNDING:** This work was supported by a grant from the MRC Network of Hubs for Trials Methodology: grant MR/L004933/1 including support from the North West Hub, London Hub, Clinical Trial Service Unit Hub, All Ireland Hub, Midlands Hub and Edinburgh Hub. The views expressed are those of the authors and not necessarily those of the MRC. The funders played no role in the study design; collection, analysis, and interpretation of data; writing of the report; or the decision to submit the article for publication. Researchers were independent of influence from study funders.

**COMPETING INTERESTS:** All authors have completed the ICMJE uniform disclosure form at [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, and no other relationships or activities that could appear to have influenced the submitted work.

**ABBREVIATIONS:** CRF, Case Report Form; CTIMP, clinical trials of investigative medicinal products; CTU, Clinical Trials Unit; IPD, Individual Participant Data; UKCRC, UK Clinical Research Collaboration

**Figure 1:** Current practice regarding data sharing policy and consent from participants to share their data

**Figure 2:** Considerations when reviewing requests for data as reported by 15 CTUs that had received a request in the past 12 months

**Figure 3:** Awareness of various data sharing initiatives and policies

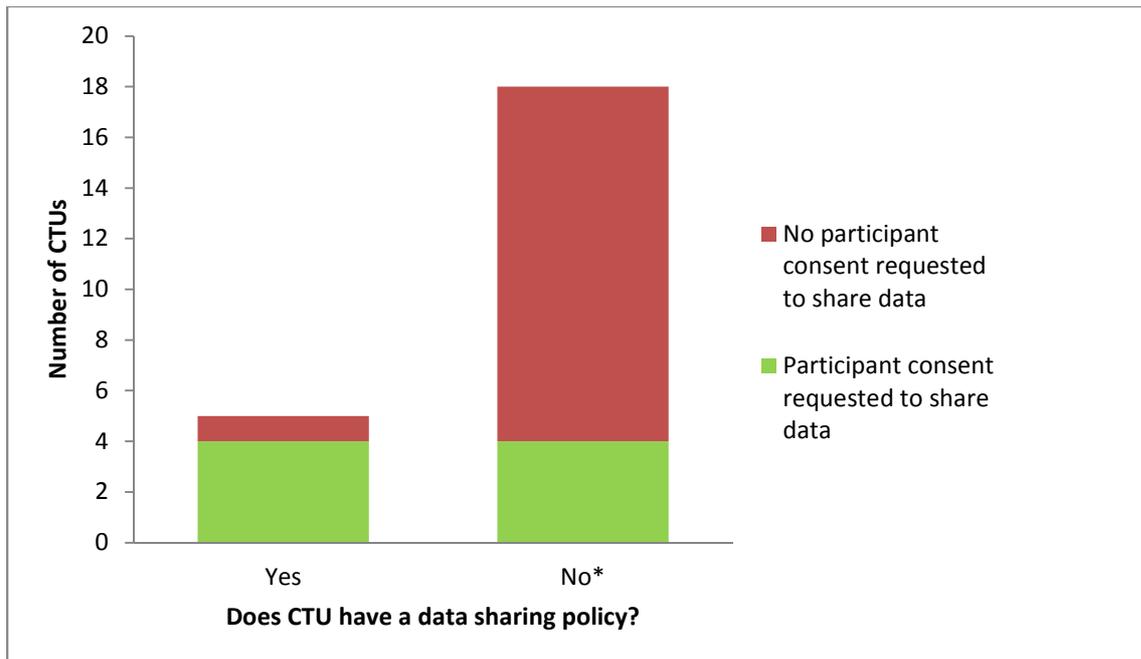
**Figure 4:** Models rated “Most suitable” by responding CTUs

**Figure 5:** Level of concern about frequently raised barriers to making full clinical trial data available on a controlled access platform

**Supplementary Material:** Survey distributed to potential respondents

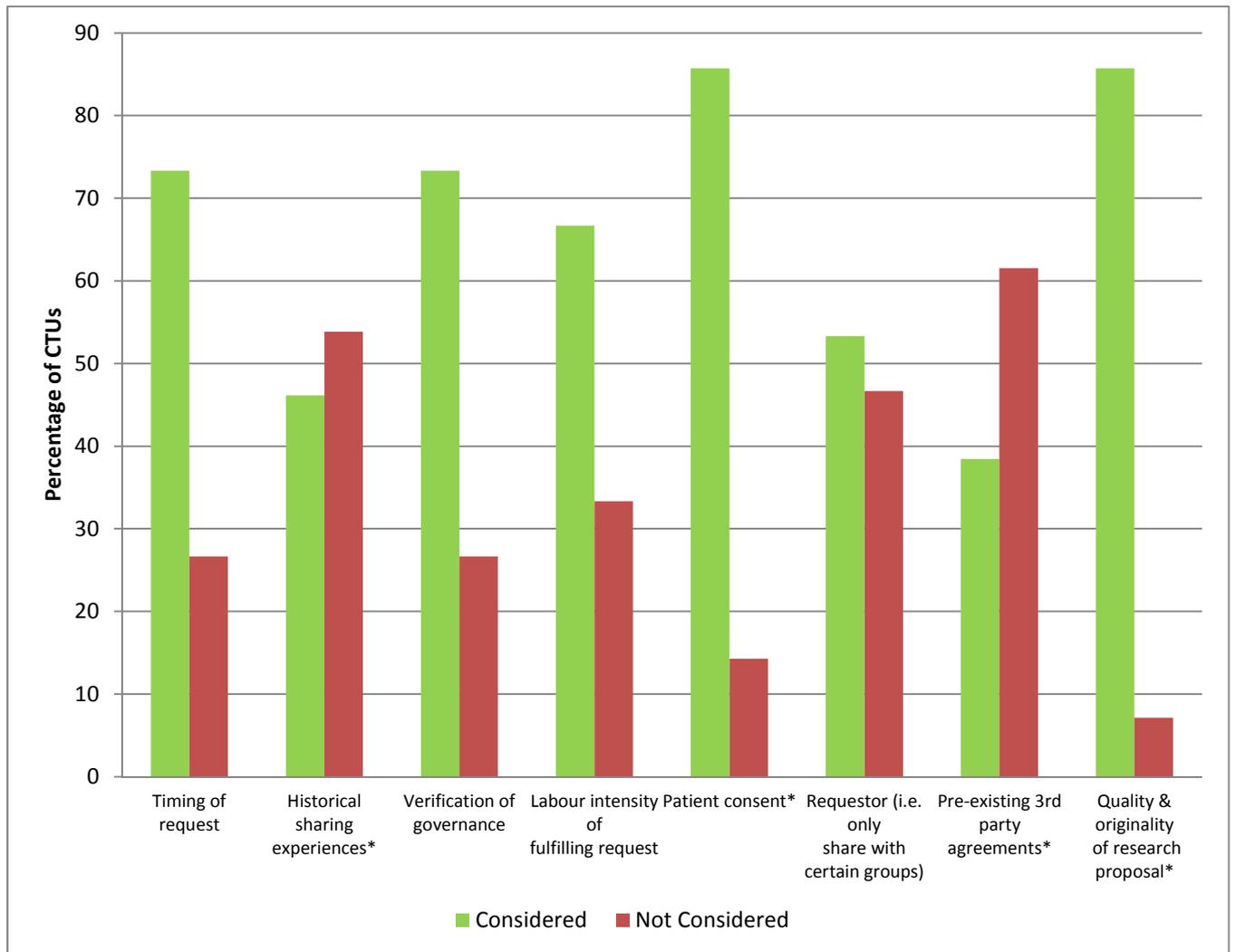
ACCEPTED MANUSCRIPT

1. Ross JS, Lehman R, Gross CP. The Importance of Clinical Trial Data Sharing: Toward More Open Science. *Circulation: Cardiovascular Quality and Outcomes*. 2012;5(2):238.
2. Gøtzsche PC. Strengthening and Opening Up Health Research by Sharing Our Raw Data. *Circulation: Cardiovascular Quality and Outcomes*. 2012;5(2):236-7.
3. Vickers A. Whose data set is it anyway? Sharing raw data from randomized trials. *Trials*. 2006;7(1):15.
4. Cooper NJ, Sutton AJ, Morris D, Ades AE, Welton NJ. Addressing between-study heterogeneity and inconsistency in mixed treatment comparisons: Application to stroke prevention treatments in individuals with non-rheumatic atrial fibrillation. *Statistics in medicine*. 2009;28(14):1861-81.
5. Lumley M, Perera D. Patient-level data: a paradigm shift in clinical trial transparency? *Interventional Cardiology*. 2013;5(6):619.
6. Gotzsche PC. Why we need easy access to all data from all clinical trials and how to accomplish it. *Trials*. 2011;12(1):249.
7. Ross JS, Krumholz HM, Ross JS, Krumholz HM. Ushering in a New Era of Open Science Through Data Sharing : The Wall Must Come Down. *JAMA*. 2013;309(13):1355.
8. Little RJ, D'Agostino R, Cohen ML, Dickersin K, Emerson SS, Farrar JT, et al. The Prevention and Treatment of Missing Data in Clinical Trials. *New England Journal of Medicine*. 2012;367(14):1355-60.
9. Doshi P, Jefferson T, Del Mar C. The Imperative to Share Clinical Study Reports: Recommendations from the Tamiflu Experience. *PLoS Med*. 2012;9(4):e1001201.
10. Lemmens T, Telfer C, Lemmens T, Telfer C. Access to information and the right to health: the human rights case for clinical trials transparency. *American Journal of Law and Medicine*. 2012;38(1):63.
11. AllTrials. AllTrials <http://www.alltrials.net/2014> [cited 2014 August]. Available from: <http://www.alltrials.net/>.
12. Agency EM. European Medicines Agency policy on publication of clinical data for medicinal products for human use. 2014.
13. ABPI. Clinical Trial Transparency: Technical standards for old, current and future clinical trials. 2013.
14. Medicine Io. Discussion Framework for Clinical Trial Data Sharing: Guiding Principles, Elements and Activities. 2014.
15. Practice EFGC. EFGCP Multi-Stakeholder Roundtable Meeting on Sharing Clinical Trial Data in the Interest of Patients and Research. 2014.
16. Godlee FGT. The new BMJ policy on sharing data from drug and device trials. *BMJ*. 2012;345.
17. Nisen P, Rockhold F. Access to Patient-Level Data from GlaxoSmithKline Clinical Trials. *New England Journal of Medicine*. 2013;369(5):475-8.
18. Site CSDR. Clinical Study Data Request Site. 2014.
19. Newswire PR. Johnson & Johnson Announces Clinical Trial Data Sharing Agreement With Yale School of Medicine. *Johnson&Johnson-YODA: Y*; 2014.
20. Rathi V, Dzara K, Gross CP, Hrynaskiewicz I, Joffe S, Krumholz HM, et al. Sharing of clinical trial data among trialists: a cross sectional survey. *BMJ (British Medical Journal)*. 2012;345(11):e7570.
21. Tudur Smith C, Dwan K, Altman DG, Clarke M, Riley R, Williamson PR. Sharing Individual Participant Data from Clinical Trials: An Opinion Survey Regarding the Establishment of a Central Repository. *PLoS ONE*. 2014;9(5):e97886.
22. Sandercock PAG, Niewada M, Członkowska A. The International Stroke Trial database. *Trials*. 2011;12.
23. Carrillo MC, Bain LJ, Frisoni GB, Weiner MW. Worldwide Alzheimer's Disease Neuroimaging Initiative. *Alzheimer's & Dementia*. 2012;8(4):337-42.
24. Cuticchia AJ, Cooley PC, Hall RD, Ying Q. NIDDK data repository: a central collection of clinical trial data. *BMC Medical Informatics & Decision Making*. 2006;6(1):19-6.
25. Hede K. Project Data Sphere to Make Cancer Clinical Trial Data Publicly Available. *Journal of the National Cancer Institute*. 2013;105(16):1159-60.
26. Gueyffier F, Boutitie F, Boissel JP, Coope J, Cutler J, Ekblom T, et al. INDANA: a meta-analysis on individual patient data in hypertension. Protocol and preliminary results. *Therapie*. 1995;50(4):353-62.
27. Consortium TB. The Biomarkers Consortium. 2014.
28. PRO-ACT. Pooled Resource Open-Access ALS Clinical Trials Database. 2011.
29. Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jeric K, et al. SPIRIT 2013 Statement: Defining Standard Protocol Items for Clinical Trials. *Annals of Internal Medicine*. 2013;158(3):200-7.
30. Data Protection Act 1998. 1998.
31. Sydes MR, Johnson AL, Meredith SK, Rauchenberger M, South A, Parmar MK. Sharing data from clinical trials: the rationale for a controlled access approach. *Trials*. 2015;16:104.
32. Sid Nair C. The Effect of Email Notification on Web-based Questionnaire Responses. *Journal for Quality & Participation*. 2013;35(4):19-23.
33. Tudur Smith C, Hopkins C, Sydes M, Woolfall K, Clarke M, Murray G, et al. Good Practice Principles for Sharing Individual Participant Data from Publicly Funded Clinical Trials. Version 1.0. <http://www.methodologyhubs.mrc.ac.uk/pdf/Datasharingguidance2015.pdf> 2015.

**Figure 1: Current practice regarding data sharing policy and consent from participants to share their data**

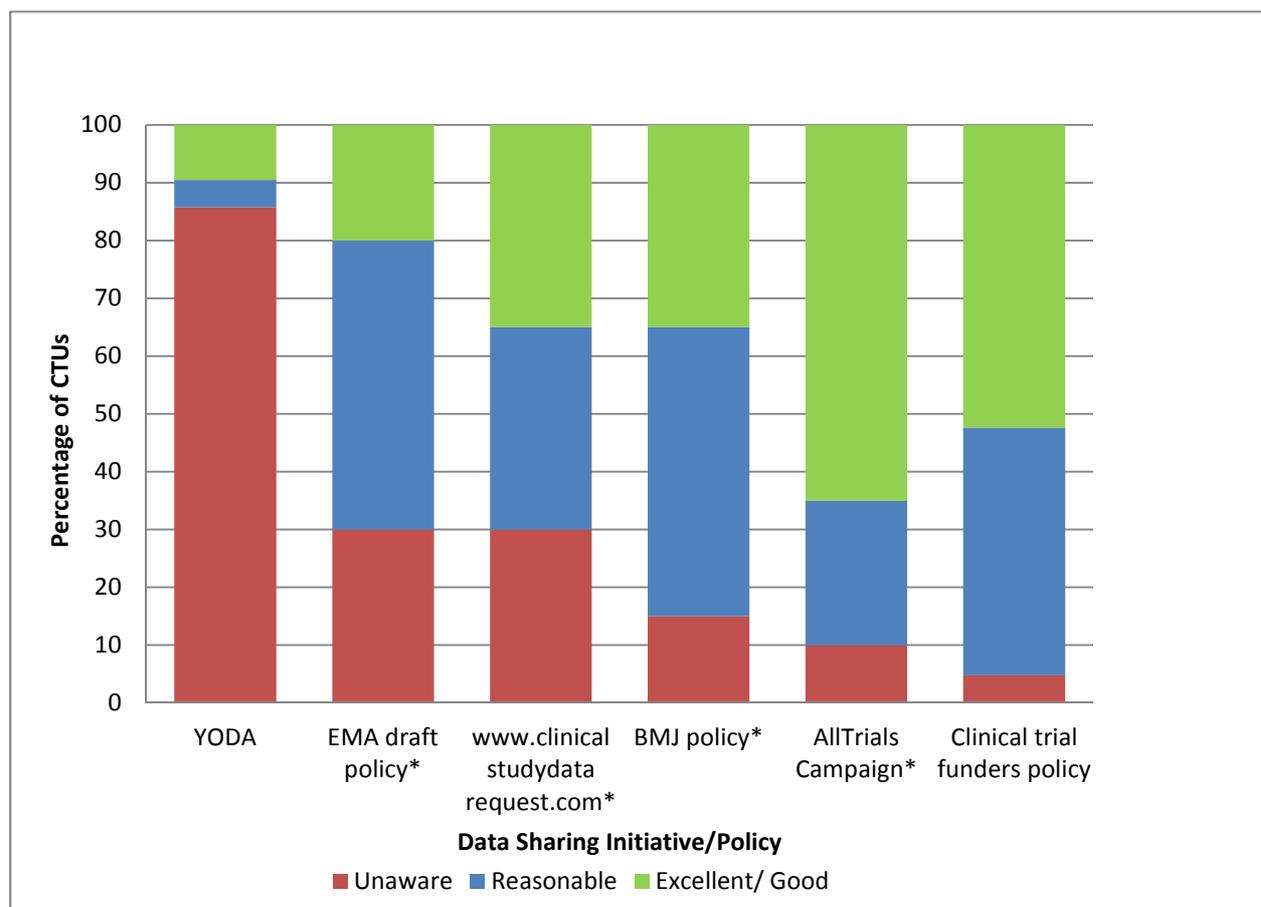
\*No policy includes 7 CTUs with no immediate intention to develop a policy and 11 CTUs with a policy in development

Figure 2. Considerations when reviewing requests for data as reported by 15 CTUs that had received a request in the past 12 months



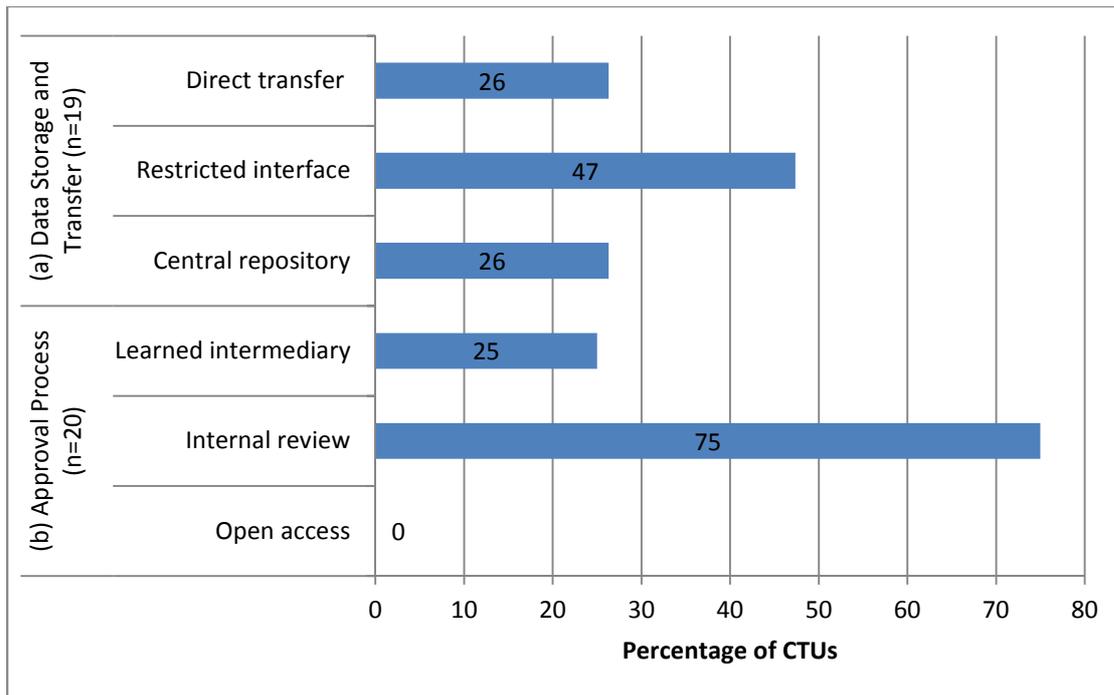
\* Total number of responses < 15 as at least one CTU did not respond

Figure 3: Awareness of various data sharing initiatives and policies



\* total response is <21 because CTUs failed to provide a response or responded N/A

Figure 4: Models rated “Most suitable” by responding CTUs



## (a) Data storage and transfer

Direct transfer: data transferred to external users for secondary analyses

Restricted interface: data remains with the data custodian but access is granted for external users to analyse data through a specific interface

Central repository: data is uploaded to, and downloaded from, a central independent repository

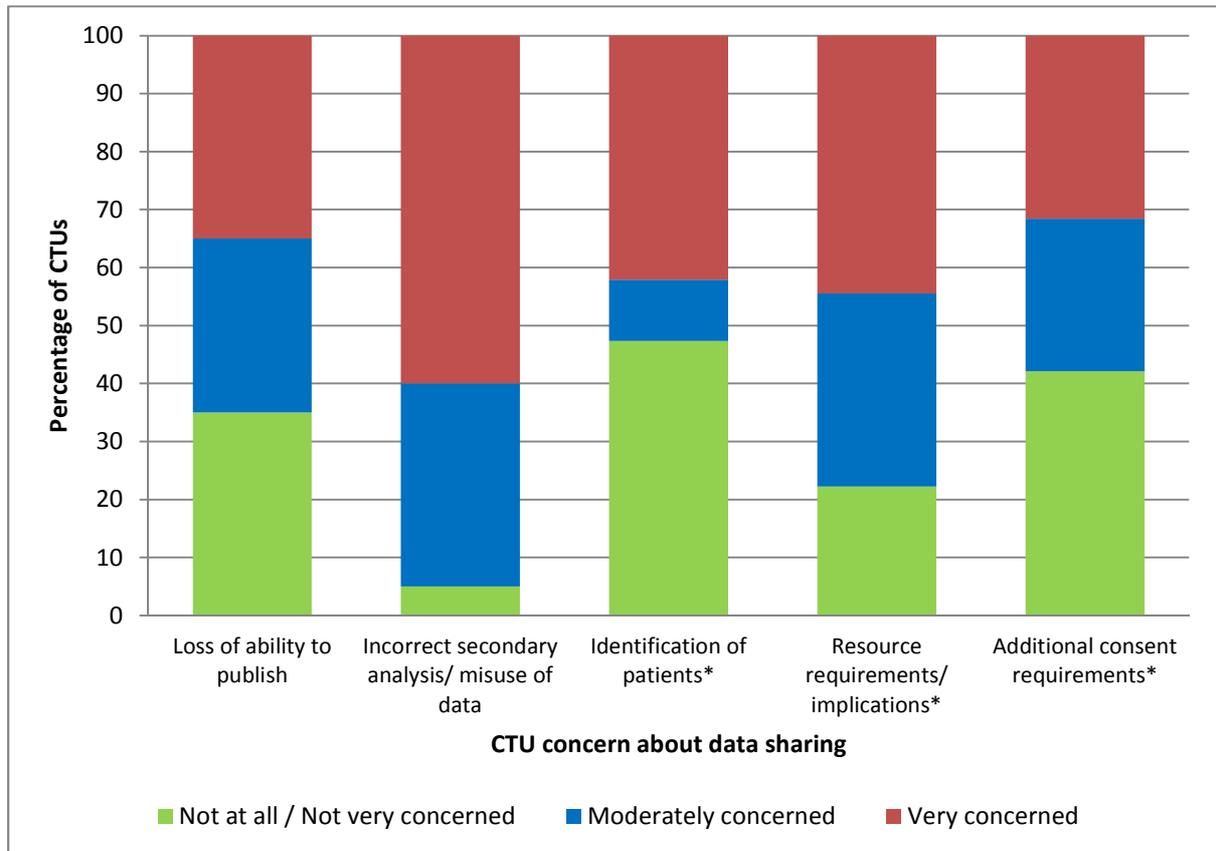
## (b) Approval process

Learned intermediary: an Independent Review Board reviews requests and judges them based on criteria such as science, benefit-risk analysis, and competence of the requestor to perform the specified analyses

Internal review: specific detailed requests are placed with the custodian who assesses the request based on science, benefit-risk analysis, and competence of the requestor to perform the specified analyses

Open access: no approval required, data available for any user to access

Figure 5: Level of concern about frequently raised barriers to making full clinical trial data available on a controlled access platform



\* total response was <20 because CTUs failed to provide a response or responded N/A

**Supplementary material: Survey distributed to potential respondents.****Purpose Of Survey**

This survey is being conducted by researchers from the MRC Hubs for Trials Methodology Research and UK CRC registered CTUs. We estimate that it will take approximately 15 minutes to complete. The survey aims to seek opinions and details of current practice related to data sharing from across the UK CRC registered CTUs. In the context of this survey, 'data' refers to the underlying individual participant data and accompanying essential documents (e.g. protocol, annotated case report forms) from a clinical trial. Results from this survey will inform the development of practical guidance on data sharing and further input will be requested from the UK CRC CTUs at a later date.

1. Name:
2. Role/Job Title:
3. Institute/Unit:

**Current Practice**

Please answer the following questions to establish a picture of the current practices utilised at your CTU.

4. Does your unit have a data sharing policy?
  - No – there is no intention to develop a policy
  - No – but there is a policy in development
  - Yes
5. Does your CTU currently adopt a consent process that specifically requests consent for patient's data to be used outside the scope of the individual clinical trial?  
*i.e. Is it made clear to the patient that their data may be used for further secondary analysis in the future?*
  - No
  - Yes
6. Would you be prepared to introduce and explain this clause to clinical trial subjects? [NOTE: Question #6 only asked of participants who answered "No" to Question #5]

**Data Sharing Requests – Experiences**

The following questions allow you to provide details of occasions when your Clinical Trial Unit has been approached with a request for access to data you have generated at your unit or are a custodian of.

7. How many requests to share data from trials your CTU has been involved in have you received in the last 12 months?
  - None
  - 1
  - 2
  - 3
  - 4
  - 5+

**Experiences Of Being Approached for Data** [NOTE; Questions #8 - #19 were not asked of participants who had answered "None" to Question #7]

Please use the questions below to give an indication of the considerations affecting the outcome of data sharing requests.

8. Who has approached your CTU with a request to access data?  
Please indicate all applicable answers.
  - NHS Trust/Clinician
  - Other UK CRC registered CTUs
  - Industry e.g. pharmaceutical company representatives
  - Institutes of higher education e.g. universities
  - Independent researcher
  - Other, please specify:

9. What reason/s were given by the requester to justify the request for data sharing?  
*If the requestor offered multiple reasons please indicate all of them.*
- Developing/Evaluating novel statistical methods
  - Meta-analysis
  - Developing study methods
  - Teaching
  - Aiding design of future clinical trials
  - Testing secondary hypotheses
  - Other, please specify:
10. Were any requests for data fulfilled?  
*'Yes' indicates that data were shared with the requester.*
- No
  - Yes
11. Please indicate below if the request/s were fulfilled completely (as per request) or partially? (*either enter "C" or "P"*) [NOTE; Question #11 only asked of participants who answered "Yes" to Question #10]
12. When assessing whether you were prepared to fulfil the request, were any of the following considered?
- |   | Yes                   | No                    | Not applicable        |
|---|-----------------------|-----------------------|-----------------------|
| Timing of request                               | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| Historical sharing experiences                  | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| Verification of governance                      | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| Labour intensity of fulfilling request          | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| Patient consent                                 | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| Requester (i.e. only share with certain groups) | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| Pre-existing third party agreements             | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| Quality and originality of research proposal    | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
13. Further to the considerations listed above, please detail any other issues that were or should have been raised when considering requests:
14. Did you have any problems transferring the data in the format required by the requester?
- No
  - Yes
15. Please indicate what the problems were? [NOTE; Question #15 only asked of participants who answered "Yes" to Question #14]
16. To assess the request for data, were you provided with any of the following:  
*Please indicate any further information/documentation provided to validate the request.*
- Research proposal outlining the purpose of the data
  - Data Sharing Agreement
  - Requester credentials / competence to analyse
  - Assurances there would be no attempt to retrospectively identify patients
  - Other, please specify:
17. In terms of labour and resources required can you compare whether the activities listed below were more difficult for historical data (>5 years old) compared to more recently generated data (within the last 5 years)?
- |   | Less difficult        | About the same        | More difficult        | Not Applicable        |
|---|-----------------------|-----------------------|-----------------------|-----------------------|
| Reviewing of request for validity                               | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| Location/Preparation of data into compatible (shareable) format | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| Anonymisation of the data                                       | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| Creating a Data Sharing Agreement                               | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| Other   | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
18. If you indicated 'other' in the question above, please indicate what other activities you refer to:

19. Based on your previous experience, can you rate the below activities in terms of their labour implications and resource intensity?

*Please define 'resource intensive' as a task that takes over 4 hours, i.e., half a day.*

	Likely to be resource intensive	Not likely to be resource intensive	Not applicable
Reviewing of request for validity	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Location/Preparation of data into compatible (shareable) format	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Anonymisation of the data	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Creating a Data Sharing Agreement	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

#### **Experiences of Requesting Data**

**Please provide details of occasions when your clinical trial unit (or individual member thereof) has approached an external data custodian with a request to access data.**

20. How many requests have been made in the last 12 months?

*Please include any data requests you are aware of from within your unit, including those requesting data for meta-analysis.*

- None
- 1
- 2
- 3
- 4
- 5+

#### **Experiences of Requesting Data (2) [NOTE; Questions #21 - #27 were not asked of participants who answered "None" to Question #20]**

**Please use these questions to indicate how successful/unsuccessful experiences with data sharing requests have been.**

21. Please indicate who the requests for data were made to:

*Please indicate all applicable answers.*

- NHS Trust/Clinician
- Other UK CRC registered CTUs
- Industry e.g. pharmaceutical company representatives
- Institutes of higher education e.g. universities
- Independent researcher
- Other, please specify:

22. Were any requests for data fulfilled?

*'Yes' indicates that data were received.*

- No
- Yes

23. If your request was denied, please indicate the reasons why:

*Please detail any reasons that were given by the data custodian for denying the request.*

24. Please indicate if your request was fulfilled:

- Completely (as per request)
- Partially (not all requested data were provided)

25. If your request was fulfilled please indicate the length of time taken to receive the data from the first request:

26. Did you have to provide any of the following to the data owner:

*Please indicate any further information/documentation you had to provide to validate your request.*

- Research proposal outlining the purpose of the data
- Data Sharing Agreement
- Requester credentials / competence to analyse
- Assurances there would be no attempt to retrospectively identify patients
- Other, please specify:

27. Please indicate the reasons for your request to access data:

*i.e. meta-analysis*

**Future Perspectives**

Please use these questions to indicate your views on the future of sharing of data within clinical trials.

28. Please rate your knowledge of the following:
- |  | Unaware               | Awareness only        | Reasonable            | Good                  | Excellent             |
|--|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| EMA Policy/0070  | <input type="radio"/> |
| All Trials Campaign  | <input type="radio"/> |
| Yale Open Data Access (YODA) Project   | <input type="radio"/> |
| GlaxoSmithKline's <a href="http://www.clinicalstudydatarequest.com">www.clinicalstudydatarequest.com</a> | <input type="radio"/> |
| BMJ Policy on Data Sharing   | <input type="radio"/> |
| Clinical trial funder's policy on data sharing   | <input type="radio"/> |
29. Further to the initiatives and policies mentioned above, are you aware of any other initiatives/data sharing policy?
- No  
 Yes
30. If yes, please briefly describe the initiative(s) below: [NOTE; Question #30 only asked of participants who answered "Yes" to Question #29]
31. In principle, would you be willing to transfer data to a centralised UK repository in the future (on the condition the repository is considered legal and ethical)?  
*i.e. within the next 2-3 years. Examples of shared platforms include [www.data-archive.ac.uk](http://www.data-archive.ac.uk) and [www.clinicaltrials.gov](http://www.clinicaltrials.gov)*
- No  
 Yes
32. Please provide a brief explanation for your answer above:  
*If your answer was 'no' please explain what assurances you would require to encourage you to say 'yes'.*

**Future Perspectives – Requirements**

This line of questioning aims to establish the requirements for a data sharing platform, with the intention of developing guidelines to streamline the process.

33. Do you have standard formats for your electronic data currently?  
*e.g. SNOMED CT, MedDRA, CDISC*
- No  
 Yes
34. Are there any specific reasons/external influences that would prevent your unit applying a standard data sharing policy?  
*'Standard' implies a data sharing policy that will be followed by all the UK CRC Registered CTUs (as a minimum)*
- No  
 Yes
35. If yes, please provide details: [NOTE; Question #35 only asked of participants who answered "Yes" to Question #34]

**Future Perspectives – Models**

If you were required to both request data from outside your CTU and also required to provide access to your CTU's individual patient data, please indicate which of the models below would you expect to be most suitable for your needs with regards to:

- 1) Data (anonymised individual patient data and associated trial documentation) transfer and storage
- 2) Approval process for data access
- 3) Timing of data access (i.e., when should data be shared?)

36. Data (anonymised individual patient data and associated trial documentation) transfer and storage models:
- Open access (*data is uploaded to, and downloaded from, a central independent repository*)
  - Access through interface (*data remains with the data custodian but access is granted for external users to analyse data through a specific interface (such as that adopted by [www.clinicalstudydatarequest.com](http://www.clinicalstudydatarequest.com))*)
  - Transfer of data to external user (*data transferred to external users for secondary analyses*)
- Please rate according to a scale based on suitability for the specific needs of the CTU you are affiliated to and only use each response once.

	Most suitable	Not quite suitable	Least suitable
Open access	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Access through interface	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Transfer to external user	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

37. Please briefly outline the main reasons for your response to the previous question:

38. If there is an option that would be more suitable for your unit, please provide it below:

39. Approval process for data access models:

Open access (*no approval required, data available for any user to access*)

Reviewed data access (*specific detailed requests are placed with the custodian who assesses the request based on science, benefit-risk analysis, and competence of the requestor to perform the specified analyses*)

Learned intermediary (*an Independent Review Board reviews requests and judges them based on criteria such as science, benefit-risk analysis, and competence of the requestor to perform the specified analyses*)

Please rate according to a scale based on suitability for the specific needs of the CTU you are affiliated to and only use each response once.

	Most suitable	Not quite suitable	Least suitable
Open access	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Reviewed data access	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Learned intermediary	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

40. Please briefly outline the main reasons for your response to the previous question:

41. If there is an option that would be more suitable for your unit, please provide it below:

42. Timing for data access (i.e. when should data be shared?)

Please indicate which timeline you think is most suitable.

- As soon as the trial is closed, data has been cleaned and final analysis has been completed
- Within 12 months after the end of the trial (defined as last patient last visit)
- Within 24 months after the end of the trial (defined as last patient last visit)
- At any time after the trial team have completed all analyses and secondary exploratory analyses
- Other, please specify:

### **Future Perspectives – Potential Problems**

There have been a number of issues highlighted that may arise from the sharing of complete clinical trial data. Please use this page to indicate your concerns and describe any problems you foresee.

43. If there was a platform where full clinical trial data were made available for sharing, how concerned would you be about the following:

	N/A	Not at all concerned	Not very concerned	Moderately concerned	Very concerned
Loss of IP/ability to publish	<input type="radio"/>				
Incorrect secondary analysis or misuse of data	<input type="radio"/>				
Identification of patients	<input type="radio"/>				
Resource requirements to ensure data were uploaded correctly (including historical data)	<input type="radio"/>				
Gaining consent from patients for research using their data outside of the specific trial they enrolled in	<input type="radio"/>				
Other	<input type="radio"/>				

44. If you indicated that you would be concerned about 'other' issues in the previous question, please briefly describe them below:

45. Please indicate any problems you foresee if there was a call for the publication of all clinical trial data (including Individual Patient Data) via a controlled access platform. Where possible, please explain what could be done to address these problems.

46. Do you have any other perspectives/comments? Please provide details:

47. Please indicate if you are happy to be contacted further about the issues of clinical trial data sharing:
- No
  - Yes

Thank you for taking the survey!

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