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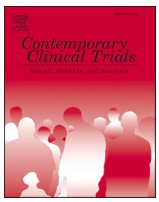

"Reality is frequently inaccurate" A case study examining the whens and whys of post-live database changes in a UK clinical trials unit *Douglas Adams

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ABSTRACT

Introduction: Accurately estimating the costs of clinical trials is challenging. There is currently no reference class data to allow researchers to understand the potential costs associated with database change management in clinical trials.

Methods: We used a case-based approach, summarising post-live changes in eleven clinical trial databases managed by Sheffield Clinical Trials Research Unit. We reviewed the database specifications for each trial and summarised the number of changes, change type, change category, and timing of changes. We pooled our experiences and made observations in relation to key themes.

Results: Median total number of changes across the eleven trials was 71 (range 40–155) and median number of changes per study week was 0.48 (range 0.32–1.34). The most common change type was modification (median 39, range 20–90), followed by additions (median 32, range 18–55), then deletions (median 7, range 1–12). In our sample, changes were more common in the first half of the trial's lifespan, regardless of its overall duration. Trials which saw continuous changes seemed more likely to be external pilots or trials in areas where the trial team was either less experienced overall or within the particular therapeutic area.

Conclusions: Researchers should plan trials with the expectation that clinical trial databases will require changes within the life of the trial, particularly in the early stages or with a less experienced trial team. More research is required to understand potential differences between clinical trial units and database types.

1. Introduction

1.1. Databases within trials

Estimating clinical trial budgets is challenging [1–3], especially at a time when protocol complexity is intensifying [4–6]. Timely completion of clinical trials is made more difficult by unplanned mid-study changes caused by unanticipated study complexities or design deficiencies [7].

Such changes must be accommodated by the clinical trial database. Trial databases are developed within a clinical trial data management system (CDMS) based on the requirements of the trial protocol and engagement with key stakeholders, especially the lead investigator(s) and statistician. Following initial development, the database will undergo user acceptance testing prior to being made live [8]. It is critical that during this process, the correct information is extracted from the protocol and other sources and that the database is tested rigorously [9,10].

1.2. The problem

There is a large amount of research focussed on database design [8], but the importance of database change management has been underreported until recently [11–13]. It is increasingly recognised that changes to the trial database become desirable or necessary because of changing user requirements, protocol updates, external circumstances, processes or procedures, or evolving software environments [12,14]. Provision for future-proofing is often built into the costs of developing software in other domains but frequently not into the development and

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maintenance of clinical trial databases [12]. Implementing such changes require the skills of both data managers and software developers [15]. However there is very little reference class data which could help a unit or trial team plan for and cost this activity, and what exists shows considerable variation and is not within a clinical trials environment [11,16,17].

As noted above, modifications to live clinical trial databases are common and can affect study timelines [15,18]. A recent global multi-sector survey ($N = 194$) of operations, data management, and other clinical trial stakeholders found that unplanned changes to databases were frequent, challenging, and time intensive [19]. Changes were related not only to the type of trial, but also due to protocol amendments and minor updates, particularly in the early years of the trials.

1.3. Aims

In this study we aim to add to the bank of reference class data available on clinical trial database changes by describing changes made to a sample of live databases, the reason for those changes, and by exploring whether there are efficiencies that could be made in the database development process. The intention is that the resulting reference class dataset will enable us to better anticipate the associated costs of different types of clinical trials from the outset.

2. Methods

To identify and classify changes made within clinical trial databases a case-based approach was adopted. Eleven clinical trials with data management provided by the Sheffield Clinical Trials Research Unit (CTRU) were selected (Table 1). CTRU is a UK Clinical Research Collaboration (CRC)-registered trials unit managing a variety of phase II and III randomised controlled trials (RCTs) across various research areas.

We included clinical trials that:

- started after September 2014;
- locked before May 2023;

We excluded any clinical trials that:

- closed early;
- were ‘database only’ (i.e. full data management not provided by CTRU);
- had a high dependency on routine data (i.e. trial was not based around prospective data collection);
- COVID studies (set-up / timelines for such studies were out of the ordinary);
- observational ‘follow up’ studies

Studies were excluded from the sample, in the main, due to their funding structure: studies which are termed ‘database-only’ differ from the included trials in having not costed for data management oversight, ongoing database changes and maintenance. Other excluded studies (routine data, observational studies, COVID) would not be expected to have the same need for database changes due to their trial / data type. Trials which closed early were excluded because their truncated timeline would not represent a true comparison to the included trials.

Data for this project were collected from database specifications provided by the data management team in Sheffield CTRU. The specifications included detailed information about each database change including, request date, name of the form affected by the change, type of change, change category (defined in Supplementary Table 1) and free text describing the nature of and/or reason for the change. For the purposes of this project, the request date has been used as the date of the change, however, the database may have been changed later as multiple individual changes are often ‘batched’ into one larger change. Information regarding the database ‘live’ and ‘lock’ dates were also provided by the data management team to allow calculation of the duration of the trials. Sheffield CTRU's CDMS includes study management reporting functionality, but each report is essentially bespoke and must be requested either upfront with the database build or as a ‘database change’ thereby attracting a similar resource cost to an amendment to the database specification. Reporting requests and changes are therefore included.

Prior to extracting the data from the specifications, it was necessary to standardise our approach to counting the changes. The main purpose of the database specification used in our sample was first to build the database and secondly to document database changes on an ongoing basis, so the data were not originally collected for this research. Therefore, there were inconsistencies in the completion of records between different staff and in the format of the specifications (e.g. use of merged cells). In order to account for these inconsistencies and to standardise our approach across all eleven trials in the sample, we took the following steps: missing fields were populated from data in the field above (to ensure no loss of data as a result of merged cells); text in date fields was amended to a comprehensible date (e.g. ‘required from database live’ was amended to the actual database live date); changes were sorted by date, form, and change type, and one change was recorded for each unique set. In some cases, changes were recorded with more than one ‘type’ but only one ‘category’. Each instance of a change ‘type’ was counted as a distinct change, i.e. if the change type recorded by the specification was ‘addition / modification’, this was counted as one addition and one modification.

We used the ‘category’ and ‘change type’ columns in the specifications to extract and tabulate changes for the following types of changes: additions, modifications, and deletions. We used the study duration (weeks) and the total number of changes to calculate the number of study changes per study week. We then extracted and tabulated changes for the following categories: branching logic (dependencies), calculated fields, field, form, point of entry validation, select (lookup) list, study management report, and ‘not categorised’. We provided medians and ranges for all change types, for the number of study changes per study week, and for the most common change categories. We rescaled the timeline from the number of weeks the database was open to a proportion of the lifespan of the study using the ‘live’ and ‘lock’ dates and 0 and 100% respectively to allow us to more easily compare the timing of changes across studies. We then graphed the temporal distribution of changes across the lifespan of the study for cross-case analysis in order to identify patterns within the sample. Between May and June 2023 the authors pooled their experiences at three one hour teleconferences and intermittent email contact. The database specifications, tabulated data, and rescaled timeline figures formed the basis of these reflections. Observations about specific points are described and discussed in the results. The observations are categorised into key themes that were derived inductively by the authors through pattern matching.

Roles vary between CTRUs, particularly in relation to data management and programming. Data managers at Sheffield CTRU perform tasks that could be categorised as both ‘data management’ and ‘programming’. They are responsible for developing trial CRFs, producing database specifications (see glossary in Supplementary Material), testing demo databases, and maintaining the live database, including managing requests for changes, which involves assessing the feasibility of the request, the impact on existing data, and testing and documenting the change. Sheffield CTRU utilises a bespoke CDMS for its clinical database, we believe this provides a higher degree of flexibility compared to off-the-shelf systems, as change requests can be considered on both the individual trial level (e.g. a change to a trial form) and on the higher system level (e.g. a change to functionality to allow a study to capture information in a new way such as the introduction of ‘entity groups’). The Sheffield data management team introduced two tools in 2017 which improved the process of constructing both database specifications and building the resultant databases. The first was eDiTH (electronic

Table 1
Details of case studies.

Study Name Design Number of centres	Management information and CTRU experience	Database open duration/ changess duration (weeks)	Population	Intervention and comparator(s)	Primary outcome
STEPWISE [20] 2-arm, parallel group, individually randomised RCT 10 centres	Full data management, Sheffield CTRU managed, CTRU prior experience with a similar: disease area = no study design = yes	144/137	18+ years with schizophrenia, schizoaffective disorder or first-episode psychosis	STructured lifestyle Education for People WIth Schizophrenia, schizoaffective disorder or first-Episode psychosis (STEPWISE) intervention or treatment as usual	Weight change after 12 months
Big CACTUS [21] 3-arm, single-blind, parallel group, individually randomised RCT 21 centres	Full data management, Sheffield CTRU managed, CTRU prior experience with a similar: disease area = yes study design = yes	169/175	18+ years with aphasia post-stroke	Daily self-managed computerised speech and language therapy plus usual care, attention control plus usual care or usual care alone	Change in word finding ability and functional communication ability
BEADS [22] 2-arm, parallel group, individually randomised, pilot RCT 3 centres	Full data management, Sheffield CTRU managed, CTRU prior experience with a similar: disease area = no study design = yes	86/70	18+ years with post-stroke depression	Behavioural activation or usual care	Feasibility: Feasibility of recruitment, acceptability of procedures, appropriateness of measures, retention of participants and potential value of conducting the main trial. Clinical: Patient Health Questionnaire (PHQ)-9 score after 6 months
PRACTICE [23] 2 × 2 factorial, parallel group, individually randomised, pilot RCT 2 centres	Full data management, Sheffield CTRU managed, CTRU prior experience with a similar: disease area = no study design = yes	53/51	35+ years admitted to hospital with Acute Exacerbations of Chronic Obstructive Pulmonary Disease (AECOPD)	Early Pulmonary Rehabilitation (EPR) in hospital, EPR at home, EPR in hospital and at home or usual care	Feasibility: Feasibility of recruitment Clinical: 6-min walk distance (6MWD) after 90 days
Endometrial SCRATCH [24] 2-arm, open-label, parallel group, individually randomised RCT 16 centres	Full data management, Sheffield CTRU managed, CTRU prior experience with a similar: disease area = no study design = yes	187/192	18–37 years undergoing their first cycle of in vitro fertilisation (IVF)	Endometrial scratch procedure or treatment as usual	Live birth after 24 weeks gestation within 10.5 months of egg collection
JtD (Journeying through Dementia) [25] 2-arm, single-blind, parallel group, individually randomised RCT 13 centres	Full data management, Sheffield CTRU managed, CTRU prior experience with a similar: disease area = yes study design = yes	148/135	People with mild dementia	Journeying through Dementia intervention plus usual care or usual care alone	Dementia related quality of life 8 months post-randomisation
OPTION-DM [26] Double-blind, individually randomised 3-period crossover RCT 13 centres	Full data management, Sheffield CTRU managed, CTRU prior experience with a similar: disease area = yes study design = no	185/120	18+ years with diabetic peripheral neuropathic pain	Amitryptiline, duloxetine, pregabalin and their combinations.	7-day average daily pain during the final week of the treatment pathway
ASPECT [27] 2-arm, parallel group, individually randomised RCT 26 centres	Full data management, Sheffield CTRU managed, CTRU prior experience with a similar: disease area = no study design = yes	171/163	7–16 years with specific phobia	One session treatment or multi-session cognitive behavioural therapy	Behavioural avoidance test scores 6-months post-randomisation
I-SOCIALISE [28] 2-arm, open-label, cluster randomised RCT 98 centres (schools)	Full data management, Sheffield CTRU managed, CTRU prior experience with a similar: disease area = no study design = no	144/142	7–15 years with a clinical diagnosis of autism	12 weeks LEGO based therapy and usual support or usual support alone	Social Skills Improvement System scale completed by unblinded teachers after 20 weeks

(*continued on next page*)

Table 1 (*continued*)

Study Name Design Number of centres	Management information and CTRU experience	Database open duration/ changess duration (weeks)	Population	Intervention and comparator(s)	Primary outcome
MSS3 [29] 2-arm, parallel group, individually randomised RCT 4 centres	Full data management, Sheffield CTRU managed, CTRU prior experience with a similar: disease area = no study design = yes	239/221	18–69 years with persistent, medically unexplained, physical symptoms	Symptoms clinic intervention plus usual care or usual care alone	Self-reported physical health questionnaire at 52 weeks post-randomisation
Up Study [30] 2-arm, double-blind, parallel group, individually randomised RCT 2 centres	Externally managed CTIMP, full data management services, CTRU prior experience with a similar: disease area = no study design = yes	126/120	18–75 years with early Parkinson's disease	Ursodeoxycholic acid 30 mg/kg or placebo	Safety and tolerability

Data dictionary for Trials in Health), first used in the OPTION-DM trial and all subsequent trials. The second was a code generator: a tool used for generating study databases from eDiTH-built specifications, which was implemented by CTRU's software developer epiGenesys. Both tools were aimed at standardising the process of producing specifications and study databases, and reducing the risk of human error.

3. Results

The median (range) total changes per trial was 71 (40–155); the median number of changes per study week was 0.48 (0.32–1.34), Supplementary Table 2. The most common type of change was modification (median 39, range 20–95), followed by additions (median 32, range 18–55), then deletions (median 7, range 0–10).

The most common category of change was field changes (median 36, range 22–79), followed by study management report changes (median 6, range 0–29), then form changes (median 6, range 2–14), Table 4. 94 changes were 'not categorised' (median 8, range 0–22). Some changes were listed in the specifications with multiple 'types' but only one 'category', resulting in minor inconsistencies in the reporting of totals between supplementary tables 2 and 3.

Figs. 1–4 show the temporal distribution of changes across the lifespan of the studies.

3.1. Change types

Additions and modifications were made in all eleven studies. Deletions were made in ten out of the eleven studies in the sample, but the total number of deletions were much lower compared to the other change types. Examples of the reasons for changes are given in Supplementary Material.

3.2. Changes which take place early in the trial lifecycle

Fig. 1 shows that a large proportion of the changes in our sample took place during the first half of the trial's lifespan, regardless of the overall duration of the study. Some trials experienced changes fairly regularly throughout the life of the trial. Some of these were pilot trials (PRACTICE, BEADS); some were trials with a lot of requests around reporting (STEPWISE, Big CACTUS) which would have seen requests largely be made at the start of the trial to aid study management.

3.3. Prior experience of the trial team / System changes

Fig. 1 shows that Endometrial SCRATCH and I-SOCIALISE required more database changes overall than the other nine studies in our sample and changes were spread across the lifetime of the study. The therapeutic area of both these trials was new to the Sheffield CTRU, which may have influenced the need for changes. In the sample we saw fewer changes in the latter half of a trial when the Sheffield CTRU team had prior experience of the therapeutic area (JtD) and/or in studies where the lead investigator was experienced in running similar trials (MSS3, Up Study).

The spike in changes seen in the ASPECT trial might also be explained through the lens of team experience. ASPECT required a number of changes to be made to one of the secondary outcome measures towards the end of trial; it is feasible that a better known therapeutic area would not have seen such changes.

The I-SOCIALISE trial also required new functionality to be added to the CTRU's CDMS. This update itself lead to a number of database changes as issues with the implementation of this functionality were ironed out.

3.4. Improvements over time

The results in Figs. 1 to 4 and Supplementary Tables 2 and 3 are presented chronologically based on the database live date. Older trials (STEPWISE, Big CACTUS) seem to have a higher number of changes compared with newer trials (JtD, OPTION-DM, MSS3), though we do see exceptions (I-SOCIALISE).

3.5. External pilot trails

Our sample included two external pilot trials, BEADS and PRACTICE. External pilot trials are small-scale, standalone studies used to assess the feasibility of a full-scale RCT, as opposed to internal pilot trials, which include the feasibility phase within the main trial. PRACTICE had 1.34 database changes per study week (the highest in the sample); BEADS had 0.80 (higher than the majority).

4. Discussion

4.1. Summary of findings

We have presented a summary of the post-database live changes made in eleven trials at one academic CTRU in order to add to reference class data for future work. Database changes were common across our sample, particularly modifications and additions. We found that the majority of changes take place in the first half of a trial, regardless of its overall duration. This is in line with previous work which describes a spike of CRF releases occurring in the first few years of a trial opening [31]. Prior experience of the trial team seems to affect the number and timing of database changes; and higher numbers of changes and a temporally wider spread of changes seem to be more common in trials

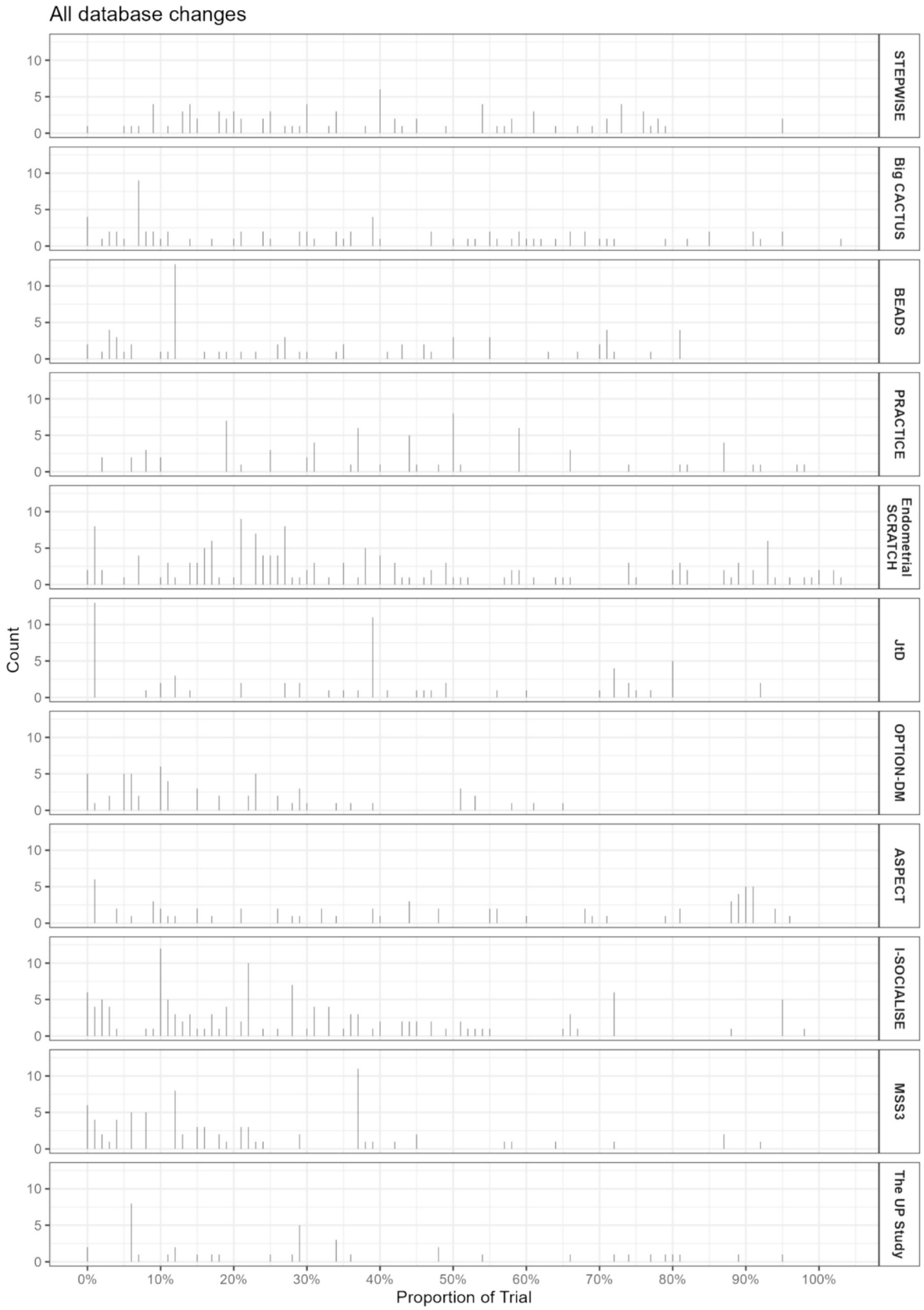

Fig. 1. All changes.

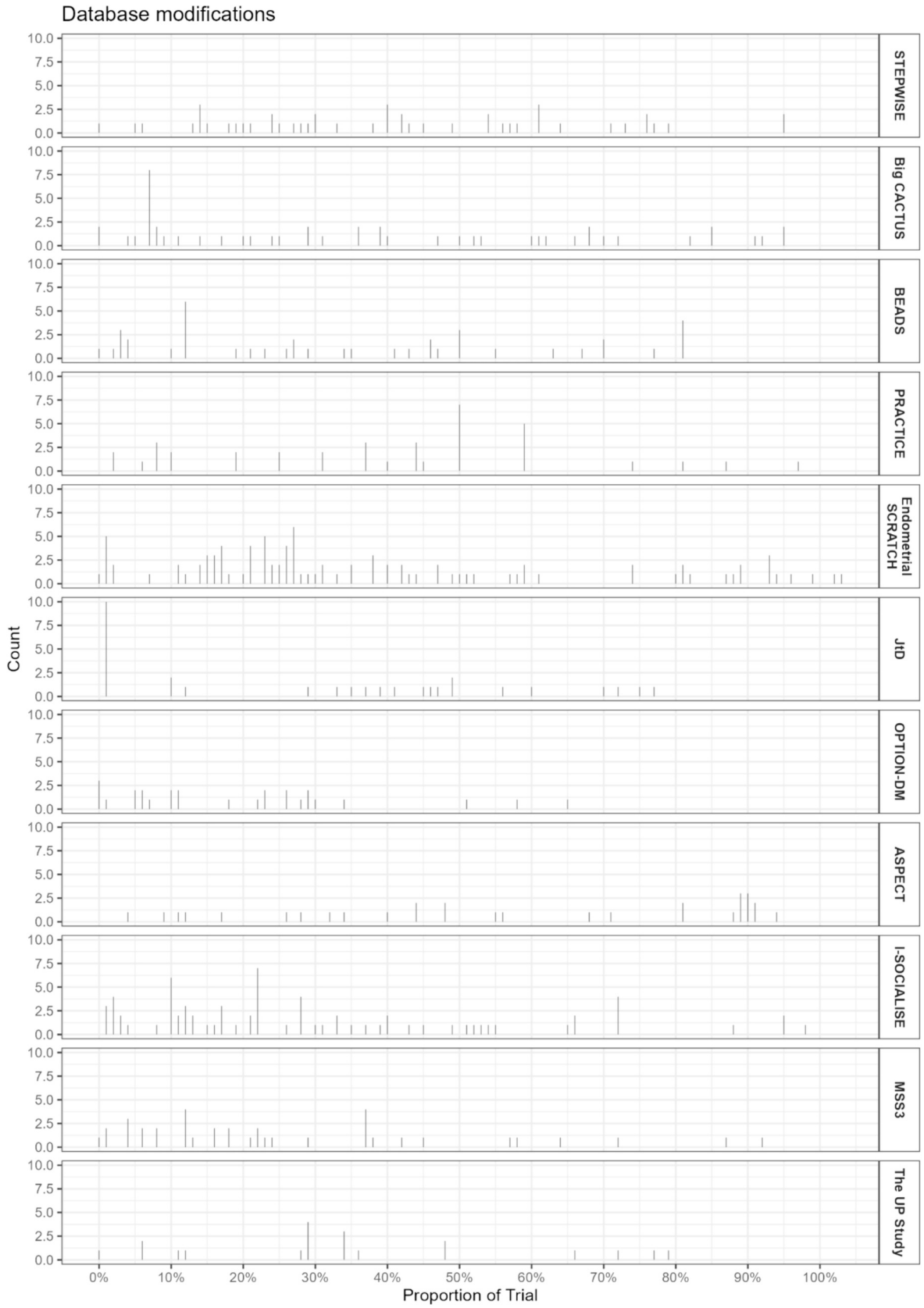

Fig. 2. Modifications.

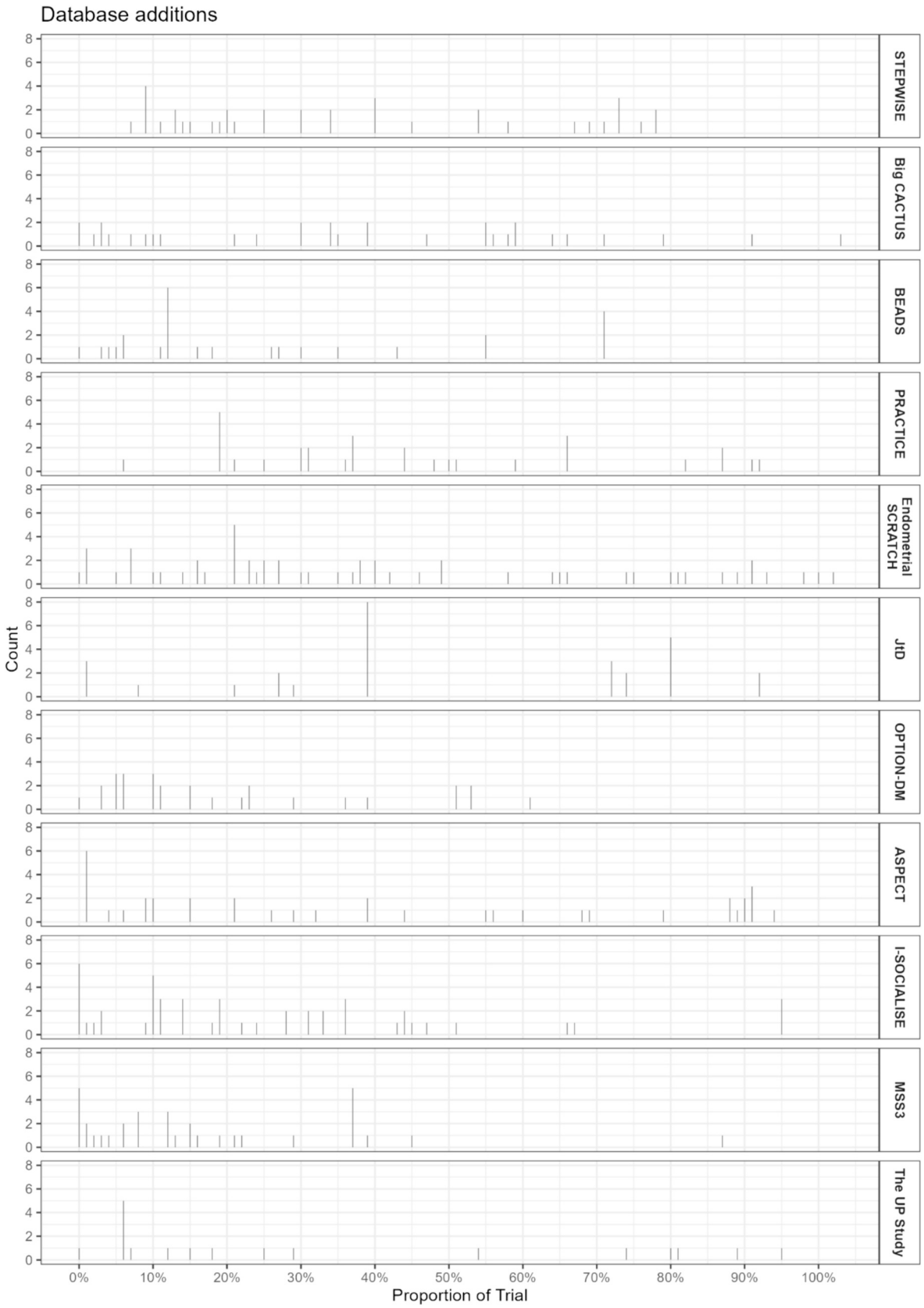

Fig. 3. Additions.

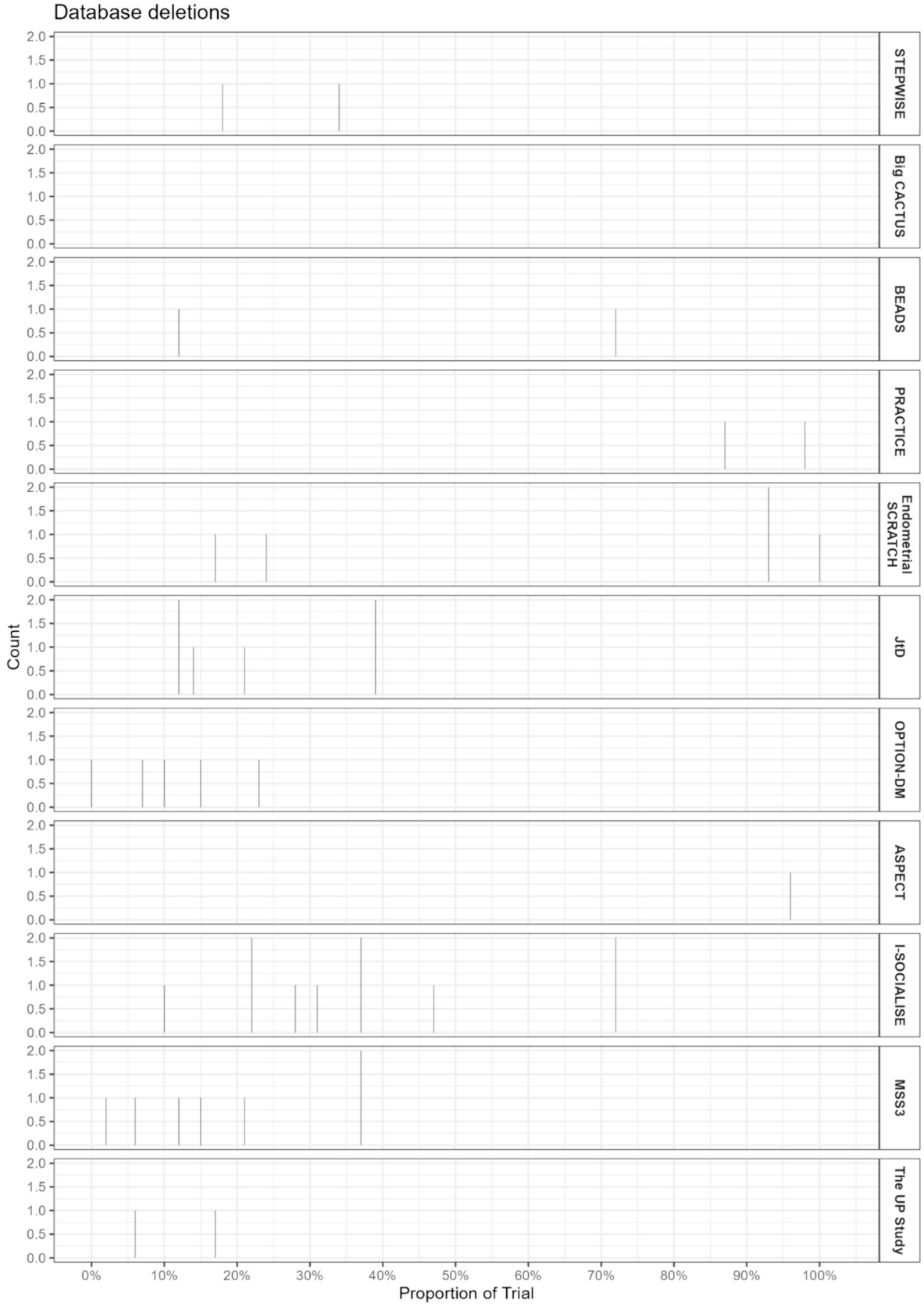

Fig. 4. Deletions.

where the CTRU was inexperienced in the therapeutic area or the lead investigator had not run previous similar trials.

Drawing on the experience of Sheffield CTRU's data managers, we have made three key observations about the possible reasons for early database changes. Firstly, the complicated process of database (and trial) set-up requires early engagement and 'buy-in' from the lead investigator and key stakeholders (study team, statisticians) as well as a well-defined protocol. These key considerations, along with robust processes, should allow data managers to accurately define database requirements and thereby prevent errors, misunderstandings, or missing information, which will need later correction. If any one of the three (early engagement; well defined protocol; robust processes) is missing, the database will likely reflect that lack. Secondly the first entry of 'real life' data into the live database may make clear previously unrecognised or unanticipated problems, such as processes which are not consistent across all sites leading to data collection issues which the database was not built to handle, or unrealistic normal range lab values. Finally, protocol amendments often arise from the experience of implementing trial procedures in the early months of recruitment, generating further database amendments. Common examples include changes or clarifications to the eligibility criteria, or making intervention procedures more flexible to accommodate variation in practice across sites.

These observations are, in essence, all drawing on the same problem of trial design: that is, that existing real life knowledge and experience (which works within a stakeholder's own context) may fail on application to trial-specific scenarios. Reality resists our expectations!

We present both changes overall and changes by type (addition, deletion, modification). Though this data is specific to our own context (CTRU, CDMS used, trial requirements) we feel it is worth drawing out the possible implications of each change type.

Deletions shown in the sample were usually field-level changes of data that were no longer required or were added in error. Some deletions (on both field and form level) were followed by an addition and so represent a correction to the data being collected. That deletions were unusual suggests either that collecting more data than required is rare, or that it does not necessarily lead to database changes.

Additions and modifications are likely to stem from similar sources: updates to the trial protocol, changes made to address genuinely unanticipated scenarios, and changes made in response to feedback, either from sites or trial stakeholders such as statisticians. If we think of modifications (and additions to a lesser extent) as refinements to an existing, robust database specification, representing changes that were required due to a trial protocol meeting real life data and implementation scenarios, we could posit that a certain number of such changes are largely inevitable. Their frequency, scale and number may be reduced by the experience gained through use of clear and tested processes, a flexible CDMS, and engagement with stakeholders, but their ubiquity perhaps underlines our wider point that, however well-planned a study is, the reality of running a trial will always throw up surprises which is important to consider when planning resources. In our sample, there seemed to be more changes in older trials (STEPWISE, Big CACTUS) than newer ones. This may in part be due to processes and Quality Control (QC) checks that were instituted after the set-up of these trials, including the Sheffield CTRU's Data Dictionary (eDiTH - electronic Data dictionary for Trials in Health) which replaced the previous method for creating databases specifications within Google Docs spreadsheets; and a QC process for double-checking specifications once they had been completed using a checklist. In addition to these QC steps within the data management function, during the period covering our sample the CTRU's software developer, epiGenesys, introduced a code generator to aid with producing databases from the specifications provided by data managers. These tools and processes reduced capacity for human error, improving the robustness of the initial database build. However, this is difficult to prove definitively from the data, as the 'Reason for change' field in the database specifications is a free text field which is not easily coded.

Our sample features two external pilot trials (BEADS and PRACTICE) which both had high numbers of changes per study week (0.80 and 1.34 respectively). This is likely to be due to the exploratory nature of pilot trials and the high likelihood that the protocol for a pilot trial will change a great deal throughout the life of the study. This must be anticipated and planned for within the trial team, including appropriately costing for the likelihood of a high number of protocol changes and resultant database changes.

Any large-scale project, such as a clinical trial or a database build, has significant potential for inaccuracy in planning and resource forecasting. One method for mitigating this is to have a store of project-specific reference class data, that is, information from comparable projects, which can guide project managers on how efficiency gains might be made [32]. As with other aspects of trial design, wide stakeholder consultation, the use of clear processes, and using tools which remove as much potential for human error as possible may mitigate the need for unanticipated database changes. However, as noted above, they are unlikely to eliminate the need for changes altogether, as reference class data is often lacking in novel situations (as shown in our sample) and projects such as trials are inherently complex with emergent properties which cannot necessarily be predicted upfront by those designing them [33,34].

The Sheffield CTRU CDMS, Prospect, allows a high degree of flexibility in its functionality, which allows it to accommodate emergent issues through the lifespan of a trial. We define flexibility here as the ability to make and test changes within a 'test' environment; push those changes to the live environment without duplicated effort; and the use of automated testing and change documentation. These features allow robust testing and efficient documentation of database changes. As Prospect is an in-house developed CDMS we also have the ability to request new functionality as required by studies and as dictated by the changing trials environment, and we have a high degree of control over system development. This flexibility is especially important in the context of an academic CTRU running a wide variety of research projects, as each therapeutic area and study design has differing data collection requirements. In comparison, a unit which specialises in a particular therapeutic area, such as oncology, may be able to use existing CRFs and database specifications from previous projects thus requiring fewer post-live database amendments.

4.2. Strengths and limitations

The current work describes the changes made to 11 systematically selected clinical trial databases over the lifespan of the trial, covering a period of 9 years. A key strength of the work is that, to our knowledge, this type of data has not been published previously and this project provides reference class data to help CTRUs plan and cost for database changes throughout the lifespan of a trial.

The results reflect the experience of a single academic CTRU and although the paper describes a range of different study types, it is unlikely to be fully representative of other UK CTRUs. In our sample, only one type of CDMS was used; it would be easier to investigate and demonstrate the impact of system flexibility if our sample had included other types of CDMS. Another limitation of the study is that the data were obtained from database specifications created to ensure the change control process was fully documented. That is to say, the data was not originally collected with the analysis we have presented in mind. It is therefore possible that there are inconsistencies within the specifications which have impacted the results. Nonetheless, the project provides a useful overview of the amount of work required to maintain a database during the life of pragmatic trials.

4.3. Implications for stakeholders

Database changes are inevitable and data management teams need to have tools and processes to be responsive to requests for changes and to

robustly document the change control process. Trial teams should expect database changes in the early stages of a clinical trial and potentially throughout the lifespan of a trial in a new therapeutic area, new type of trial design, or with an inexperienced team. Staff involved in costing clinical trials and funders should be aware of the ongoing requirement for post-live database changes and the potential impact this has on workload for the data management team throughout the trial.

If funders are basing their willingness-to-pay on a per-participant threshold [35] then it will often be difficult to contain the costs of external pilot trials because they are necessarily exploratory, not just with regard to issues such as effect sizes but also in terms of clinical processes. They will often need to accommodate large numbers of changes, as we have empirically demonstrated. Funders should therefore consider the fixed cost of the trials unit rather than simply looking at the per participant costs.

4.4. Implications for further research

Further research to obtain reference class data in other settings is needed, for example from other CTUs. In particular, understanding the potential differences between a bespoke CDMS such as the one used by Sheffield CTRU and an off-the-shelf system. More work is required to understand the reasons for post-live database changes and to investigate potential improvements in the initial database design process. It would also be beneficial to better understand how database changes affect the end product provided to trial statisticians for analysis and whether the additional work required to make post-live database changes improves data quality for the final analysis.

5. Conclusion

Researchers should expect the need for changes to the design of clinical trial databases in the early stages of recruitment and follow-up. These may be more likely where the team are inexperienced, more generally or in the specific topic area. The use of 'real-life' data during database testing and close collaboration with key study team members during CRF and database development is recommended to reduce the need for post-live database changes.

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CRediT authorship contribution statement

Jennifer Petrie: Writing – original draft, Visualization, Methodology. **Amanda Loban:** Writing – review & editing, Resources, Methodology. **Emily Turton:** Writing – review & editing, Resources, Methodology. **Julia Derebecka:** Writing – review & editing, Methodology. **Siobhán North:** Writing – review & editing, Supervision, Methodology. **Esther Herbert:** Writing – review & editing, Visualization. **Daniel Hind:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The authors do not have permission to share data.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cct.2024.107573.

References

[1] Tufts Center for the Study of Drug Development, Cost Variation and Mis-Estimation Characterize Clinical Trial Budgets, Particularly in Early Phases, 2022.
[2] D. Hind, B.C. Reeves, S. Bathers, C. Bray, A. Corkhill, C. Hayward, et al., Comparative costs and activity from a sample of UK clinical trials units, Trials 18 (1) (2017) 203. Available from: https://doi.org/10.1186/s13063-017-1934-3.
[3] T.J. Moore, J. Heyward, G. Anderson, G.C. Alexander, Variation in the estimated costs of pivotal clinical benefit trials supporting the US approval of new therapeutic agents, 2015{\textendash}2017: a cross-sectional study, BMJ Open 10 (6) (2020). Available from: https://bmjopen.bmj.com/content/10/6/e038863.
[4] Tufts Centre for the Study of Drug Development, Protocol Complexity and Patient Enrollment Intensify Challenges in Oncology Trials, 2021.
[5] Tufts Center for the Study of Drug Development, Rising Protocol Complexity is Hindering Study Performance, Cost, and Efficiency, 2018.
[6] Tufts Center for the Study of Drug Design, Protocol Design Scope and Execution Burden Continue to Rise, Most Notably in Phase III, 2023.
[7] Tufts Centre for the Study of Drug Development, Planned and Unplanned Mid-Study Updates Pose Major Challenge to Clinical Trial Timelines, 2021.
[8] B. Krishnankutty, S. Bellary, N.B.R. Kumar, L.S. Moodahadu, Data management in clinical research: an overview, Indian J Pharmacol. 44 (2) (2012) 168–172.
[9] M. Sydes, K. Gillies, P. Williamson, ICTMC 2022: 6th International Clinical Trials Methodology Conference – book of abstracts [Internet]. Masters L, Love S, Townsend S, Diaz-Montana C, Schiavone F, Tappenden N, Rauchenberger M. Right data, right time: presenting a new tool for extracting data management requirements from clinical trial protocols. Zenodo, 2023. Available, from, https://doi.org/10.5281/zenodo.7741866.
[10] G. Clayton, K. Pike, R. Nash, D. Hutton, C. Rogers, Improving the efficiency of testing database functionality through statistical involvement, Trials 16 (2) (2015) P30. Available from: https://doi.org/10.1186/1745-6215-16-S2-P30.
[11] V. Holt, M. Ramage, K. Kear, N. Heap, The usage of best practices and procedures in the database community, Inf. Syst. 49 (2015) 163–181.
[12] N. Lammari, J. Akoka, I. Comyn-Wattiau, in: D. Konstantas, M. Léonard, Y. Pigneur, S. Patel (Eds.), Supporting database evolution: Using ontologies matching BT - object-oriented information systems, Springer Berlin Heidelberg, Berlin, Heidelberg, 2003, pp. 284–288.
[13] Meeting abstracts from the 4th International Clinical Trials Methodology Conference (ICTMC) and the 38th Annual Meeting of the Society for Clinical Trials. Rauchenberger M, Babigumira K, Borg C, Little E, Tappenden N, Sydes M, Van Looy N. Will you walk a little faster? - joining the database development dance, Trials 18 (1) (2017) 200. Available from, https://doi.org/10.1186/s13063-017-1902-y.
[14] C. Mullins, The Complete Guide to DBA Practices and Procedures, Addison Wesley, Upper Saddle River, New Jersey, 2012.
[15] C.A. Brandt, S. Argraves, R. Money, G. Ananth, N.M. Trocky, P.M. Nadkarni, Informatics tools to improve clinical research study implementation, Contemp. Clin. Trials 27 (2) (2006) 112–122.
[16] D. de Vries, J.F. Roddick, The case for mesodata: an empirical investigation of an evolving database system, Inf Softw Technol [Internet]. 49 (9) (2007) 1061–1072. Available from: https://www.sciencedirect.com/science/article/pii/S0950584906001881.
[17] D. Sjøberg, Quantifying schema evolution, Inf Softw Technol 35 (1) (1993) 35–44. Available from: https://www.sciencedirect.com/science/article/pii/0950584993900027Z.
[18] S. Bellary, B. Krishnankutty, M.S. Latha, Basics of case report form designing in clinical research, Perspect. Clin. Res. 5 (4) (2014) 159–166.
[19] B. Harper, Z. Smith, J. Snowdon, R. DiCicco, R. Hekmat, V. Willis, et al., Characterizing pain points in clinical data management and assessing the impact of mid-study updates, Ther. Innov. Regul. Sci. 55 (5) (2021) 1006–1012.
[20] R.I.G. Holt, R. Gossage-Worrall, D. Hind, M.J. Bradburn, P. McCrone, T. Morris, et al., Structured lifestyle education for people with schizophrenia, schizoaffective disorder and first-episode psychosis (STEPWISE): randomised controlled trial, Br. J. Psychiatry 214 (2) (2019) 63–73.
[21] R. Palmer, M. Dimairo, C. Cooper, P. Enderby, M. Brady, A. Bowen, et al., Self-managed, computerised speech and language therapy for patients with chronic aphasia post-stroke compared with usual care or attention control (big CACTUS): a multicentre, single-blinded, randomised controlled trial, Lancet Neurol. 18 (9) (2019) 821–833.
[22] S.A. Thomas, A.E. Drummond, N.B. Lincoln, R.L. Palmer, R. das Nair, N.R. Latimer, et al., Behavioural activation therapy for post-stroke depression: the BEADS feasibility RCT, Health Technol. Assess. 23 (47) (2019) 1–176.

[23] M. Cox, C. O'Connor, K. Biggs, D. Hind, O. Bortolami, M. Franklin, et al., The Feasibility of Early Pulmonary Rehabilitation and Activity after COPD Exacerbations: External Pilot Randomised Controlled Trial, Qualitative Case Study and Exploratory Economic Evaluation vol. 22, Health Technol Assess, 2018, p. 242. Available from: https://doi.org/10.3310/hta22110.
[24] M. Metwally, R. Chatters, M. Dimairo, S. Walters, C. Pye, D. White, et al., A randomised controlled trial to assess the clinical effectiveness and safety of the endometrial scratch procedure prior to first-time IVF, with or without ICSI, Hum Reprod [Internet]. 36 (7) (2021) 1841–1853. Available from: https://doi.org/10.1093/humrep/deab041.
[25] G.A. Mountain, C.L. Cooper, J. Wright, S.J. Walters, E. Lee, C. Craig, et al., The Journeying through Dementia psychosocial intervention versus usual care study: a single-blind, parallel group, phase 3 trial, Lancet Heal Longev 3 (4) (2022) e276–85.
[26] S. Tesfaye, G. Sloan, J. Petrie, D. White, M. Bradburn, S. Julious, et al., Comparison of amitriptyline supplemented with pregabalin, pregabalin supplemented with amitriptyline, and duloxetine supplemented with pregabalin for the treatment of diabetic peripheral neuropathic pain (OPTION-DM): a multicentre, double-blind, randomis, Lancet (London, England). 400 (10353) (2022) 680–690.
[27] B. Wright, L. Tindall, A.J. Scott, E. Lee, C. Cooper, K. Biggs, et al., One session treatment (OST) is equivalent to multi-session cognitive behavioral therapy (CBT) in children with specific phobias (ASPECT): results from a national non-inferiority randomized controlled trial, J Child Psychol Psychiatry 64 (1) (2023) 39–49. Available from: https://acamh.onlinelibrary.wiley.com/doi/abs/10.1111/jcpp.13665.
[28] B. Wright, E. Kingsley, C. Cooper, K. Biggs, M. Bursnall, H.I. Wang, et al., I-SOCIALISE: results from a cluster randomised controlled trial investigating the social competence and isolation of children with autism taking part in LEGO(®) based therapy ('Play brick therapy') clubs in school environments, Autism 27 (8) (2023), 13623613231159700.
[29] C. Mooney, D.A. White, J. Dawson, V. Deary, K. Fryer, M. Greco, et al., Study protocol for the multiple symptoms study 3: a pragmatic, randomised controlled trial of a clinic for patients with persistent (medically unexplained) physical symptoms, BMJ Open [Internet]. 12 (11) (2022). Available from: https://bmjopen.bmj.com/content/12/11/e066511.
[30] T. Payne, M. Sassani, E. Buckley, S. Moll, A. Anton, M. Appleby, et al., Ursodeoxycholic acid as a novel disease-modifying treatment for Parkinson's disease: protocol for a two-Centre, randomised, double-blind, placebo-controlled trial, the "UP" study, BMJ Open 10 (8) (2020) e038911.
[31] D. Hague, S. Townsend, L. Masters, M. Rauchenberger, N. Van Looy, C. Diaz-Montana, et al., Changing platforms without stopping the train: experiences of data management and data management systems when adapting platform protocols by adding and closing comparisons, Trials 20 (1) (2019) 294. Available from: https://doi.org/10.1186/s13063-019-3322-7.
[32] B. Flyvbjerg, Curbing optimism Bias and strategic misrepresentation in planning: reference class forecasting in practice, Eur Plan Stud [Internet]. 16 (1) (2008) 3–21. Available from: https://doi.org/10.1080/09654310701747936.
[33] S. Bullock, D. Cliff, Complexity and Emergent Behaviour in ICT Systems, 2004.
[34] V. Holt, A Study into Best Practices and Procedures Used in the Management of Database Systems, Available from: http://oro.open.ac.uk/50950/, 2017.
[35] T. Stafford, I. Rombach, D. Hind, B. Mateen, H.B. Woods, M. Dimario, et al., Where next for partial randomisation of research funding? The feasibility of RCTs and alternatives, Wellcome Open Res. (2023) 8.