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Change The Study Protocol To Rescue A Trial - When / why/ challenges

Ronit Haviv, PhD
SrVP Clinical, QA and Regulation
Cordio Medical
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The voice of care


YOUR
FIRST AMENDMENT
NEEDS
YOU


FREEDOM OF SPEECH

Patient's voice is captured by the smartphone app/voice based digital assistance and sent for analysis

A real-time voice/speech analysis workflow detects early buildup of fluids in the patient's lungs before the appearance of clinical symptoms

Alerts are generated once a pre-defined threshold is crossed

Overview

01

WHY

Protocol modification may be necessary to rescue a trial or respond to changed circumstances

02

CAUSE

Amendments are perceived as a largely unavoidable problem

A. **When** is protocol change necessary?

B. What are the key **challenges** to be managed?

C. What are the underlying problems that **cause** them?

D. Can they be **avoided**?

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Protocol amendments are frequent

Tufts Center for the Study of Drug Development

The Tufts Center for the Study of Drug Development (Tufts CSDD) 2022

- **76% trials** require **one or more** amendments

  Since 2015 the **prevalence** increased from **60% to 76%** AND the **mean** number of amendments per **protocol** has increased by **60% (from 2.1 to 3.3)**

- **40%** of protocol amendments occur even **before first** patients are enrolled!

- Leads to significant unplanned **expense** and **delay**.

  The time from **identifying** the need-to-amend to last oversight approval now takes an average of **>8M** or 260 days.
  The total average duration to **implement** an amendment (**>7M** or 215 days)
  - Tripled in the last decade

- The **high incidence** of protocol amendments is likely to **continue**

New Benchmarks on Protocol Amendment Practices, Trends and their Impact on Clinical Trial Performance Original Research
Published: 04 March 2024

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354 Amendment changes

Amendment Changes

Rank	Category	Number
1	Addition of sites [a,b,c]	61
2	More details added for clarity [a,b,c]	50
3	Extension [a,c]	42
4	Who carries out trial tasks [b,c]	37
5	Change of named staff [b,c]	23
6	Additional instructions added [c]	21
7	Document corrections for consistency [c]	19
7	Change to recruitment pathway [b]	19
8	Increase in sample size [a]	18
8	Timepoints when outcome measures are taken [b,c]	18
9	Change from specific to generic wording [a,c]	17
9	Remove specific named procedures [c]	17
10	Alternative methods of communication with participants [b,c]	16

Reasons for Amendments

Rank	Category	Number
1	To achieve recruitment target [a,b]	39
2	Approval of newly created documents	31
3	To allow flexibility [a]	19
4	For participant's convenience	18
5	To collect more data to add to findings [a,b]	15
6	To accommodate different procedures at other sites [a]	11
7	Staff no longer working on trial	9
7	Oversight committee's recommendation [b]	9
8	Updates so in line with recommended guidelines	8
9	Feedback from staff at sites [a]	7
9	Not feasible to carry out requirements	7
10	Not receiving complete data from all patients [b]	5
10	Following analysis results [a]	5

Fig. 2 Content analysis findings displaying the most common content categories for amendment changes and reasons for amendments.

N.B. Content categories that had the same frequency count were ranked the same. This visual also integrates data gathered from the interviews; the content categories are annotated with feedback from the interviewees after viewing these findings, where some interviewees had stated that **a** they commonly see these categories, **b** they see less of these categories and **c** these categories could have been avoided


Trials

RESEARCH Open Access

Common Clinical Trial Amendments, why they are submitted and how they can be avoided: a mixed methods study on NHS UK Sponsored Research (Amendments Assemble)

Shivam Joshi

Protocol amendments are frequent

Across all trials…

- Two-thirds (77%) of amendments had causes that sponsor companies considered **unavoidable**

  amendments that were the result of **new safety** information, new **regulatory** requests, changes in the **standard of care**, or study **objectives**

- One-quater (23%) were considered **partially or completely avoidable**

  Undetected **design** flaws, **inconsistencies**, or **errors** in the protocol, and difficulties **recruiting** study volunteers were rated as amendment causes that sponsors could have better **anticipated** and avoided.

- The total average duration to **implement an amendment** has nearly **tripled** during the past decade

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Classification of Amendments

Substantial or Non-Substantial

"**Substantial**" where they are likely to have a significant impact on…

- the **safety** or **physical** or **mental** integrity of the subjects, or
- the **scientific value** of the trial, or
- the **conduct** or **management** of the trial, or
- the **quality or safety** of any **IMP** used in the trial.

Otherwise, they are "non-substantial"

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Classification of Amendments

Substantial amendments May need authorization Before Implementation

01

Urgent safety measures (such as temporarily halting the trial to **protect** participants against any immediate hazard)

- **may be taken without prior authorisation**
- but must be reported to **the health authorities and Ethics Committee**

02

All other substantial amendments

- **health authority authorisation must be sought before** the amendment is implemented

Non-substantial amendments
do not have to be reported to authorities, but should be recorded and be **available** upon request for **inspection** centrally and at the trial site

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Classification of Amendments

All protocol Amendments necessary to Rescue a trial Will be “Substantial”

Imagine…

An **un**anticipated **safety** issue has arisen that **impacts inclusion/exclusion** criteria or requires a new **procedure** for safety monitoring

New information about the **disease** or **treatment** suggests alterations are needed to the **protocol tests or schedule**

Patient recruitment and enrollment issues threaten trial **success**

What are the key challenges to be managed?

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The Key challenges to be managed

1. Approval
   a) Submission to Health Authorities
   b) Submission to IEC/IRB

2. Administrative issues
   a) Contract or insurance changes
   to administrative systems
   itation

Cost?

3. Protecting **data** outcomes
   l considerations
   b) Changes to data collection and handling
   c) Changes to legacy data

Not surprisingly an amendment is estimated to cost a **$1m** to implement

4. Local implementations
   a) Single site amendment
   b) Global amendment roll-out by country and site

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Managing the challenges

1. Approval

a) Submission to Health Authorities

- Notification of amendment **form**
- If **the risk/benefit** assessment of the study been affected, how do the changes impact the trial
- **Highlighted changes** to the protocol and associated documentation are

Reply from Health Authorities (Within **35 days)**

1. **acceptance** of the amendment,
2. acceptance subject to **conditions**, or
3. grounds for **non-acceptance** of the amendment (usually requiring a resubmission)

b) Submission to <u>each Ethics</u> Committee/IRB

- As for authorities
- Changed supporting documents e.g. informed consent

Approval needed before implementation of changes at each site

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Managing the challenges

2. Administrative issues

a) Contract or insurance

b) Administrative systems

- eCRF/CTMS/study management tool
- Investigator portals
- TMF

c) Documentation

- Trial specific procedures
- Study/site aids
- Informed consent

d) Training

- Internal staff
- Site staff

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Managing the challenges

3. Protecting data outcomes

a) Statistical considerations

- Often gets **overlooked**
- Not obvious that an alteration to one **non-statistical section of the protocol** can have an impact on the statistics.

Example

Relaxing of inclusion/exclusion criteria to speed enrolment.

- **Enlarges** the target (changed) patient population
- Can make the uncertainty in the estimate of the **treatment effect** larger and lower the power of the study
- May mean the sample size should be increased

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Managing the challenges

3. Protecting data outcomes

b) Changes to data collection and handling

- Updates needed to data collection instruments to reflect protocol changes
  - Paper **CRFs**… updated, reprinted, distributed, incorporated into existing books
  - **eCRF**/ePRO… new programming, testing, patching
- Data verification **routines** must be adapted and distributed
- **Backend systems** modified to accept new data, **validate**, **report**

c) Changes may need to be applied to legacy/existing data

Managing the challenges

4. implementations

a) **Single site amendment**

b) **Global amendment being implemented by country or even site**

Navigating the need for change in different environment/economies

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Underlying problem

clinical research professionals largely **perceive** protocol amendments as a major and unavoidable **problem**

But amendments are just the solution for (examples):

1. **Cycle time pressures that leave inadequate time for planning**
2. **Clinical trials having become more complex**
3. **The growing difficulty to meet patient recruitment goals**

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Underlying problem / Cause amendments

1 Cycle time pressures that leave inadequate time for planning

- Reflect judgments made and **risks** taken, by **management** to meet ever **tighter deadlines and budgets**.
- Faced with time pressures, project teams must often **move forward with risks** (new trends in **standards of care**, results from other **trials not yet reported**…).

The number of avoidable amendments (23%) **AND** the high percentage of amendments before first patient enrol (43%)

Suggest the need for better upfront protocol planning and review.

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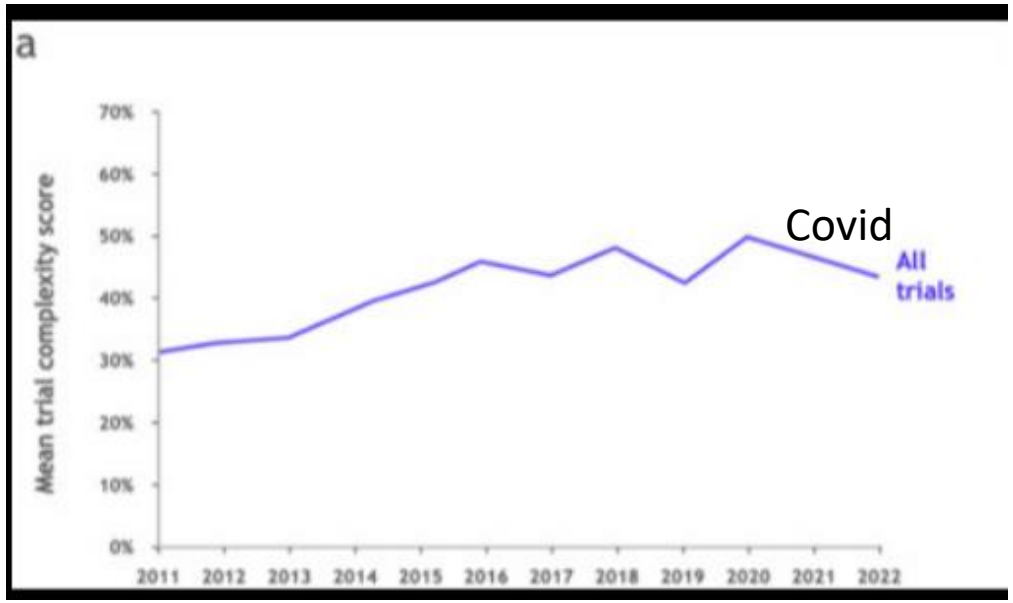
underlying problem / cause amendments

2 Clinical trials have become more complex

Trial complexity is increasing over time*



- More procedures
- More work
- Longer
- Harder to enrol

More effort and cost!

* Clinical trials are becoming more complex: a machine learning analysis of data from over 16,000 trials
Nigel Markey, et al. Sci Rep. 2024 Feb 12;14(1):3514.

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Underlying problem / Cause amendments

3 **Meeting patient recruitment goals has become more difficult**

- 65-80% of clinical trials don't meet their **timelines**, largely due to challenges in patient **recruitment**
- 30% of trial **sites** fail to **enrol** even a single patient
- Only **4%** of US or European populations **participate** in clinical trials
- Only 1 out of 20 patients (**5%**) who respond to clinical trial recruitment promotions **enrol** in a study

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Underlying problem / Cause amendments

As a result

- Trial completion is frequently **delayed** to extend the recruitment period
- **Extra sites** are recruited to compensate for low performers
- **Frequent changes** in the study protocol are require to **rescue** trials
- In the worst case… the **trial fails** to achieve its **scientific** goal or is **abandoned** having put patients needlessly at **risk**

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Avoiding Protocol Change

~23-30% of protocol changes could have been avoided and saved countless dollars (TUFTS CSDD)

Avoid amendments by investing in…

1) Optimization of protocol **design**
2) Better country and site **selection**
3) **Regional** optimization (seasonal, medical, competition)
4) **Support** for local **recruitment** planning
5) Better risk management
6) Performance monitoring during the study

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Summary

- Protocol amendment is a **frequent** occurrence
- **Rescuing** a trial through substantial modification of the protocol may be **unavoidable in certain circumstances:**
  - Recruitment threatens **trial success**
  - An unanticipated **safety** issue
  - Local **IECs** requirement
  - **New information** about the **disease** or **treatment**
- Protocol amendment though is a **costly solution**
  - **Modification** has key **challenges** that must be **managed**
  - In particular we must ensuring changes do not **compromise data quality**
- **Many** amendments are **avoidable**

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THANK YOU!

For any questions:

ronit@cordio-med.com

Tel: 052-2400877

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