Failure to Report Protocol violations in Clinical Trials:

A Threat to Internal Validity?

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Protocol Violation/Deviation

- *DEFINITIONS:*

  Protocol Violation:

  A departure from the guidelines specified in the study protocol that could have been prevented by the investigator

Wolf GT, Makuch RW: Editorial: A classification system for protocol deviations in clinical trials. *Cancer Clin Trials* 1980, 3:101-103.

Protocol Violation/Deviation

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  Protocol Violation:

  A departure from the guidelines specified in the study protocol that could have been prevented by the investigator

  Protocol Deviation:

  A departure from the study protocol due to patient safety reasons

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Background

- Preventable errors in study conduct (protocol violations) may lead to the introduction of systematic and random errors into a clinical trial that ultimately results in flawed conclusions.

DiFrancesco R, Rosenkranz SL, Craft J, Morse GD: Tutorial reduces protocol deviations in multicenter ACTG trials with pharmacology endpoints. HIV Clinical Trials 2006, 7:203-209.

Background

- Preventable errors in study conduct (protocol violations) may lead to the introduction of systematic and random errors into a clinical trial that ultimately results in flawed conclusions.
- There is no general agreement on what constitutes appropriate thresholds for acceptable and excessive protocol violation rates in clinical trials.

Background

- Preventable errors in study conduct (protocol violations) may lead to the introduction of systematic and random errors into a clinical trial that ultimately results in flawed conclusions.
- There is no general agreement on what constitutes appropriate thresholds for acceptable and excessive protocol violation rates in clinical trials.
- One authority on the conduct of clinical trials suggests that PVs in more than 10% of enrolled patients is *excessive*.

3. Pocock SJ: Protocol Deviations. In Clinical Trials: A practical approach. Edited by: Pocock SJ. New York: John Wiley 1983: 176-186.

Purpose of this Project

- To gain a better understanding of reported protocol violation rates in clinical trials

Sweetman EA & Doig GS: Failure to report protocol violations in clinical trials: a threat to internal validity? *Trials* 2011; 12: 214-221.

Methods

- We reviewed 80 consecutive trials in 4 major journals (20 in each of NEJM, The Lancet, JAMA & BMJ)

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  Study Selection

  - Consecutive clinical trials published after May 1st 2009 were eligible.
  - All identified abstracts were independently reviewed by 2 authors (EAS, GSD).
  - Any abstract constituting a clinical trial was retrieved in full.
  - Cluster and individual patient randomised trials were eligible.
  - Subgroup analyses, economic analyses and previously published trials were not eligible.

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  Trial Characteristics

  - Study type (cluster, factorial), patient population, study Intervention, number of patients randomised, number of study sites, funding source of trial, reporting of trial education/start up processes, response to PVs, adherence to GCP guidelines, reporting of randomisation, blinding and allocation concealment, management structure (management, steering committee), PV types, PV rates and methods used to reduce and prevent PVs.

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Protocol Violation (Types)

Identified, Defined and Reported on 5 Types of PVs

1) ***Enrolment PV***

2) ***Randomisation PV***

3) ***Study Intervention PV***

4) ***Patient Compliance PV***

5) ***Data Collection PV***

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1) ***Enrolment PV*** – A member of the research team failed to appropriately apply the study's eligibility criteria.

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4) ***Patient Compliance PV*** – Study participants failing to comply with the trial protocol regarding a study intervention or other requirements of participation in a trial.
5) ***Data Collection PV*** – Encompassed errors in which the research team failed to comply with pre-specified trial guidelines for data collection and/or outcome evaluation due to avoidable reasons.

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Results

Characteristics of Included Clinical Trials:

Median number of trial participants: 701 (range 20 – 162 367)

Median number of participating sites: 15 (range 1 - 701)

Median study duration: 24 months (range 5.81 - 127)

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Median number of participating sites: 15 (range 1 - 701)

Median study duration: 24 months (range 5.81 - 127)

19% (15/80) of trials were single centre

74% (59/80) of trials were academically funded

65% (52/80) of trials reported a significant positive effect, 32% (26/80) neutral & 2.5% (2/80) significant harm.

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Methodological Quality of Included Clinical Trials:

Reporting of Allocation Concealment	
Maintained	52.5% (42/80)
Unclear	45.0% (36/80)
Not maintained	2.5% (2/80)
Use of Any Type of Blinding	58.75% (47/80)
Presentation of Results According to ITT	71.25% (57/80)

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Protocol Violation Reporting

Explicit reporting of PVs varied widely according to type:

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Enrolment PV

- 10/80 (12.5%) of trials provided explicit reporting

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- 7/80 (7.7%) of trials provided explicit reporting

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- 7/80 (7.7%) of trials provided explicit reporting

Study Intervention PV

- 17/80 (21.2%) of trials provided explicit reporting

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Randomisation PV

- 7/80 (7.7%) of trials provided explicit reporting

Study Intervention PV

- 17/80 (21.2%) of trials provided explicit reporting

Patient Compliance PV

- 38/80 (47.5%) of trials provided explicit reporting

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Randomisation PV

- 7/80 (7.7%) of trials provided explicit reporting

Study Intervention PV

- 17/80 (21.2%) of trials provided explicit reporting

Patient Compliance PV

- 38/80 (47.5%) of trials provided explicit reporting

Data Collection PV

- 17/80 (21.2%) of trials provided explicit reporting

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Conclusions

- We conducted a comprehensive review of 80 clinical trials in 4 major journals to gain a better understanding of protocol violation reporting.

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Conclusions

- We conducted a comprehensive review of 80 clinical trials in 4 major journals to gain a better understanding of protocol violation reporting.
- Overall we found protocol violation reporting to be *poor*.

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Recommendations

- We believe that the CONSORT statement should highlight the importance of PVs by making reporting requirements more explicit:

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Recommendations

- We believe that the CONSORT statement should highlight the importance of PVs by making reporting requirements more explicit:
  - Reporting on each PV by type (Enrolment, Randomisation, Study Intervention, Patient Compliance, Data Collection)
  - Distinguish between protocol violations (preventable) vs protocol deviations (safety)

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- Clinical trialists should embrace Wolf's definition of a protocol violation because it incorporates the concept of causality which allows a trialist to identify protocol violations that are *preventable*.
- We recommend that Journal Editors should require full reporting of protocol violations.
- Full reporting is the first step towards improving our understanding of the influence of *excessive* PVs on the results of clinical trials.

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Questions?

Thank you very much for your time.

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