Departure from treatment protocol in published RCTs: a review

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Departures from treatment protocol

- Departures from treatment protocol (DTP)
  - Includes nonadherence on part of participant and health provider

- Various forms of DTP in RCTs
  - Non-receipt of allocated treatment
  - Switching trial treatments
  - Nonadherence to treatment dose/schedule
  - Treatment interruptions
  - Permanent discontinuation of treatment

Benefit analysis: efficacy vs effectiveness

- ITT: effectiveness of treatment
  - Include all participants as randomised
  - Effect of *policy* of prescribing treatment rather than efficacy
- PP: efficacy of treatment
  - Based on compliers rather than randomised groups
  - Selection bias: balance across groups is lost
- Randomisation-based efficacy estimators (White 2005)
  - Based on comparison of treatment groups as randomised
  - Treatment effect varies according to amount of treatment received

Harms analysis

- Appropriate harms analysis population in presence of DTP
  - ITT?
    - No (CONSORT 2001)
    - Yes (CONSORT extension for harms 2004)
    - No comment (CONSORT 2010)
  - According to treatment received
    - ICH GCP E3 and E9

Review of RCTs

- Aim:
  - Ascertain extent to which the issue of DTP is reported and addressed in analyses of current RCTs
- Methods:
  - 100 RCTs published in BMJ, NEJM, JAMA, Lancet in 2008
  - Determine
    - quality of reporting on DTP
      - CONSORT flow diagrams/text
    - nature of DTP reported
    - statistical methods used to deal with DTP
      - benefit outcomes
      - harms outcomes

Quality of reporting

- Variable quality of reporting in CONSORT flow diagram (96) or text
  - Treatment initiation
    - 42 did not state how many started randomised treatment
  - Treatment completeness
    - 80 (of 88 trials with longitudinal treatment periods) gave some information on treatment completeness
      - Persistence
        - Completed/discontinued treatment: 43 trials
      - Adherence (over treatment period)
        - Participant adherence: 29 trials
        - Adherence of treatment providers: 4 trials (of 57 with treatment administered by health care provider)

Quality of reporting

- Terminology not always clear
  - “Withdrew”
  - “Lost to follow up”
  - “Completed study protocol”
  - “Protocol deviations”
  - Discontinuation due to certain events
  - Completion of different aspects of treatment reported separately
  - Number completing treatment overall, not by treatment group
  - Adherence of treatment provider: impact on treatment received by patient?

Adequate reporting on treatment

- Adequacy of reporting depends on treatment duration
  - Single treatment
    - Treatment receipt
      - Number who received intervention
  - Short term intervention period
    - Treatment initiation and completion (assuming treatment interruptions unlikely)
      - Number who initiated intervention
      - Number who completed intervention
  - Long term intervention period
    - Treatment initiation, persistence and adherence
      - Number who initiated intervention
      - Number who persisted with intervention to end of intervention period
      - Measure of adherence over intervention period

Adequate reporting on treatment

- Single one-off treatment
  - Treatment receipt: 83% (10/12)
- Short term intervention period
  - Treatment initiation and completion: 36% (8/22)
- Long term intervention period
  - Treatment initiation and persistence: 35% (23/66)
  - Treatment initiation, persistence and adherence: 11% (7/66)

Nature of DTP reported

- 98 reported some form of DTP
  - non-receipt of allocated treatment (39)
  - incomplete treatment (in those who initiated allocated treatment) (78)
  - nonadherence to treatment dose/schedule (23)
  - switching trial treatments (12)
  - starting open label treatment (7)
  - starting disallowed/non-trial treatment (4)
  - nonadherence by treatment providers (12)

Benefit analysis

- 50 (51%) used methods to deal with DTP in benefit analysis
  - Variation of PP: 46
    - Primary analysis: 18
    - Primary “ITT” or “modified ITT” analysis: 23
    - Sensitivity analysis: 13 (including 1 case of IPCW)
      - IPCW: Inverse probability of censoring weighting method (Robins 2000)
    - Subgroup analysis: 2
    - Unlabelled analysis: 1
  - As treated analysis: 3
  - DTP indicates treatment failure: 2
  - Time to treatment failure is trial outcome: 4

Harms analysis

- 72 trials mentioned harms outcomes or assessments
- 69 (96%) presented a harms analysis
  - Specifically defined harms analysis population: 26 (38%)
    - Actual treatment received: 18
    - “ITT”: 5
    - Started treatment: 2
    - Completed treatment: 1
  - Did not explicitly specify harms analysis population: 43 (62%)
    - Apparently analysed as per benefit outcomes: 33 (31 “ITT”, 2 PP)
    - No analysis population defined for harms or benefit outcomes: 9
    - Stated “safety population” without further definition: 1

Relevance

- 12 trial reports explicitly discussed issue of DTP

"...relatively high rates of discontinuation in the active treatment arm and crossover to active treatment in the placebo arm are a limitation of the study..."

"....decreasing compliance is a major contributor to the apparent plateauing of effect..."

"...the results presented here may underestimate the magnitude of both adverse effects and beneficial effects among women who adhere to treatment..."

"In general, with the advent of ever more effective second and third-line therapies as cancer treatments, and the growing use of crossover designs, it is becoming increasingly difficult to detect improvements in overall survival in confirmatory phase III studies."

Conclusions

- DTP is common in RCTs but data presented may be ambiguous or scant
  - Especially treatment initiation and discontinuation
- Trialists often attempt to handle DTP using variations of PP analysis
  - “ITT” population often excludes patients due to DTP
  - DTP recognised by some trialists as an important issue that may lead to biased treatment effects
  - Randomisation-based methods not typically used
- Confusion over appropriate population for harms outcomes

Recommendations

- Trialists:
  - Report numbers initiating, completing and adhering to intervention in each randomised group (as appropriate, depending on treatment duration)
    - Report number "receiving" treatment only if single one-off treatment; otherwise report number "initiating" treatment
    - Report number "completing" treatment only if short term intervention; if long term intervention, described with the number who "persist" with intervention to the end of intervention period along with measure of adherence over intervention period.
  - Report withdrawal, loss to follow up, protocol deviations, etc explicitly with respect to treatment received
  - If any participants are excluded from analysis, trialists must justify this decision and discuss how their omission may bias results.

Recommendations

- Need for wider dissemination of randomisation-based methods for analysis of benefit outcomes

- Explicit guidance needed on analysis of harms outcomes in presence of DTP
  - Still within the remit of CONSORT?
    - “Note that the CONSORT 2010 Statement does not include recommendations for designing, conducting, and analysing trials. It solely addresses the reporting of what was done and what was found.” (Schulz 2010)

References

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White IR (2005) Uses and limitations of randomization-based efficacy estimators. *Statistical Methods in Medical Research* 14:327-347