

Appendix 1 for Doshi P, Jefferson T. Clinical study reports of randomised controlled trials:an exploratory review of previously confidential industry reports. *BMJ Open* 2013;3:e002496. doi:10.1136/bmjopen-2012-002496 <http://dx.doi.org/10.1136/bmjopen-2012-002496>

Appendix 1. Elements specified ICH E3 “Structure and Content of Clinical Study Reports” (1995)*

1. TITLE PAGE
2. SYNOPSIS
3. TABLE OF CONTENTS FOR THE INDIVIDUAL CLINICAL STUDY REPORT
4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS
5. Ethics
 - 5.1. Independent Ethics Committee (IEC) or Institutional Review Board (IRB)
 - 5.2. Ethical conduct of the study
 - 5.3. Patient information and consent
6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE
7. INTRODUCTION
8. STUDY OBJECTIVES
9. INVESTIGATIONAL PLAN
 - 9.1. Overall study design and plan – description
 - 9.2. Discussion of study design, including the choice of control groups
 - 9.3. Selection of study population
 - 9.3.1. Inclusion criteria
 - 9.3.2. Exclusion criteria
 - 9.3.3. Removal of Patients from Therapy or Assessment
 - 9.4. Treatments
 - 9.4.1. Treatments Administered
 - 9.4.2. Identity of Investigational Product(s)
 - 9.4.3. Method of Assigning Patients to Treatment Groups
 - 9.4.4. Selection of Doses in the Study
 - 9.4.5. Blinding
 - 9.4.6. Prior and Concomitant Therapy
 - 9.4.7. Treatment Compliance
 - 9.5. Efficacy and safety variables
 - 9.5.1. Efficacy and Safety Measurements Assessed and Flow Chart
 - 9.5.2. Appropriateness of Measurements

* International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Structure and Content of Clinical Study Reports: E3 [Internet]. 1995 http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_Guideline.pdf (accessed 8 July 2012)

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9.5.3. Primary Efficacy Variable(s)

9.5.4. Drug Concentration Measurements

9.6. Data quality assurance

9.7. Statistical methods planned in the protocol and determination of sample size

9.7.1. Statistical and Analytical Plans

9.7.2. Determination of Sample Size

9.8. Changes in the conduct of the study or planned analyses

10. STUDY PATIENTS

10.1. Disposition of patients

10.2. Protocol deviations

11. EFFICACY EVALUATION

11.1. Data sets analyzed

11.2. Demographic and other baseline characteristics

11.3. Measurements of treatment compliance

11.4. Efficacy results and tabulations of individual patient data

11.4.1. Analysis of efficacy

11.4.2. Statistical/analytical issues

11.4.2.1. Adjustments for covariates

11.4.2.2. Handling of Dropouts or Missing Data

11.4.2.3. Interim Analyses and Data Monitoring

11.4.2.4. Multicentre Studies

11.4.2.5. Multiple Comparison/Multiplicity

11.4.2.6. Use of an "Efficacy Subset" of Patients

11.4.2.7. Active-Control Studies Intended to Show Equivalence

11.4.2.8. Examination of Subgroups

11.4.3. Tabulation of Individual Response Data

11.4.4. Drug Dose, Drug Concentration, and Relationships to Response

11.4.5. Drug-Drug and Drug-Disease Interactions

11.4.6. Drug Dose, Drug Concentration, and Relationships to Response

11.4.7. By-Patient Displays

12. SAFETY EVALUATION

12.1. Extent of exposure

12.2. Adverse events (AES)

12.2.1. Brief Summary of Adverse Events

12.2.2. Display of Adverse Events

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12.2.3. Analysis of Adverse Events

12.2.4. Listing of Adverse Events by Patient

12.3. Deaths, other Serious Adverse Events and Other Significant Adverse Events

12.3.1. Listing of Deaths, other Serious Adverse Events and Other Significant Adverse Events

12.3.1.1. Deaths

12.3.1.2. Other Serious Adverse Events

12.3.1.3. Other Significant Adverse Events

12.3.2. Narratives of Deaths, Other Serious Adverse Events and Certain Other Significant Adverse Events

12.3.3. Analysis and Discussion of Deaths, Other Serious Adverse Events and Other Significant Adverse Events

12.4. Clinical laboratory evaluation

12.4.1. Listing of Individual Laboratory Measurements by Patient (16.2.8) and Each Abnormal Laboratory Value (14.3.4)

12.4.2. Evaluation of Each Laboratory Parameter

12.4.2.1. Laboratory Values Over Time

12.4.2.2. Individual Patient Changes

12.4.2.3. Individual Clinically Significant Abnormalities

12.5. Vital signs, physical findings and other observations related to safety

12.6. Safety conclusions

13. DISCUSSION AND OVERALL CONCLUSIONS

14. TABLES, FIGURES, AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

14.1. Demographic data

14.2. Efficacy data

14.3. Safety data

14.3.1. Displays of Adverse Events

14.3.2. Listings of Deaths, Other Serious and Significant Adverse Events

14.3.3. Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events

14.3.4. Abnormal Laboratory Value Listing (Each Patient)

15. REFERENCE LIST

16. APPENDICES

16.1. Study Information

16.1.1. Protocol and protocol amendments

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- 16.1.2. Sample case report form (unique pages only)
- 16.1.3. List of IECs or IRBs (plus the name of the committee Chair if required by the regulatory authority) - Representative written information for patient and sample consent forms
- 16.1.4. List and description of investigators and other important participants in the study, including brief (1 page) CVs or equivalent summaries of training and experience relevant to the performance of the clinical study
- 16.1.5. Signatures of principal or coordinating investigator(s) or sponsor's responsible medical officer, depending on the regulatory authority's requirement
- 16.1.6. Listing of patients receiving test drug(s)/investigational product(s) from specific batches, where more than one batch was used
- 16.1.7. Randomisation scheme and codes (patient identification and treatment assigned)
- 16.1.8. Audit certificates (if available)
- 16.1.9. Documentation of statistical methods
- 16.1.10. Documentation of inter-laboratory standardisation methods and quality assurance procedures if used
- 16.1.11. Publications based on the study
- 16.1.12. Important publications referenced in the report
- 16.2. Patient Data Listings
 - 16.2.1. Discontinued patients
 - 16.2.2. Protocol deviations
 - 16.2.3. Patients excluded from the efficacy analysis
 - 16.2.4. Demographic data
 - 16.2.5. Compliance and/or drug concentration data (if available)
 - 16.2.6. Individual efficacy response data
 - 16.2.7. Adverse event listings (each patient)
 - 16.2.8. Listing of individual laboratory measurements by patient, when required by regulatory authorities
- 16.3. Case Report Forms
 - 16.3.1. CRFs for deaths, other serious adverse events and withdrawals for AE
 - 16.3.2. Other CRFs submitted
- 16.4. Individual Patient Data Listings (US Archival Listings)