Publication writing and real world evidence

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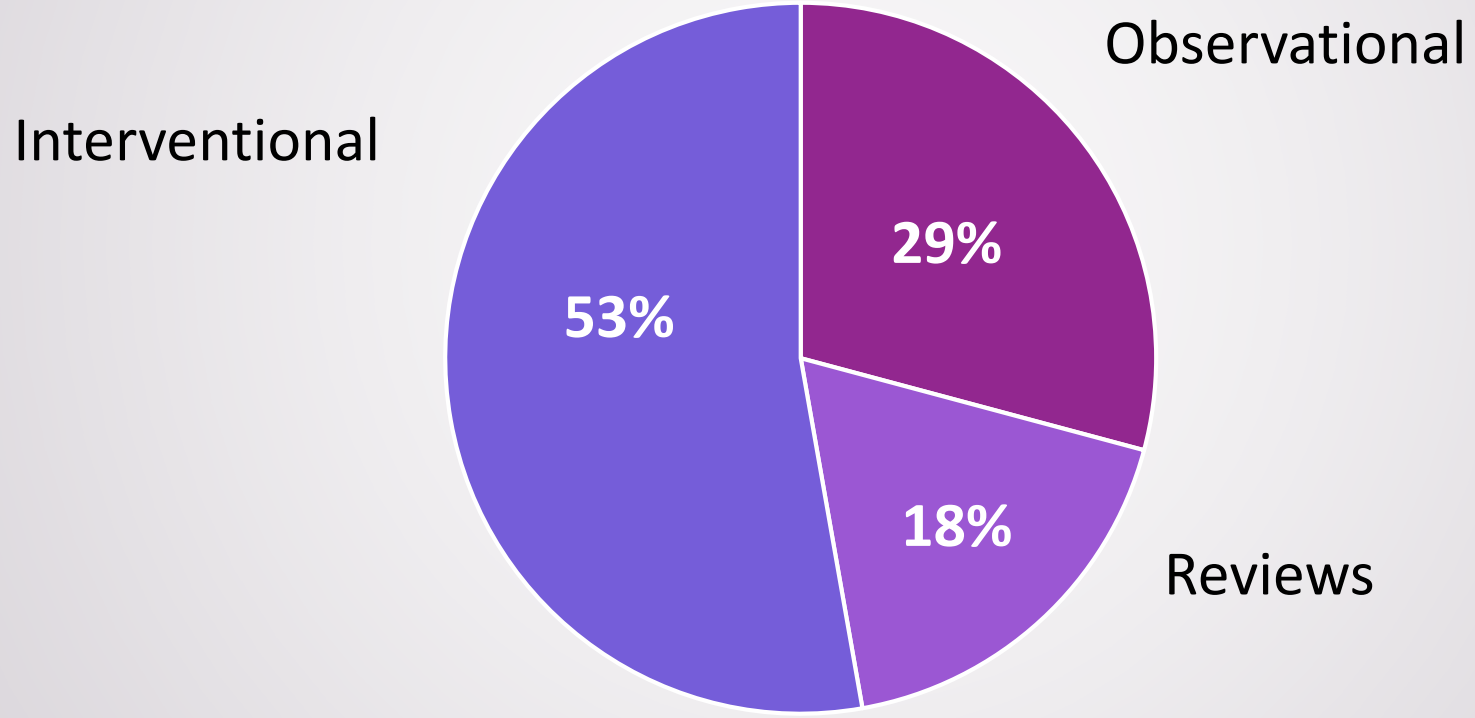
Publication mix



Based on 72 publications from 2004 to 2018

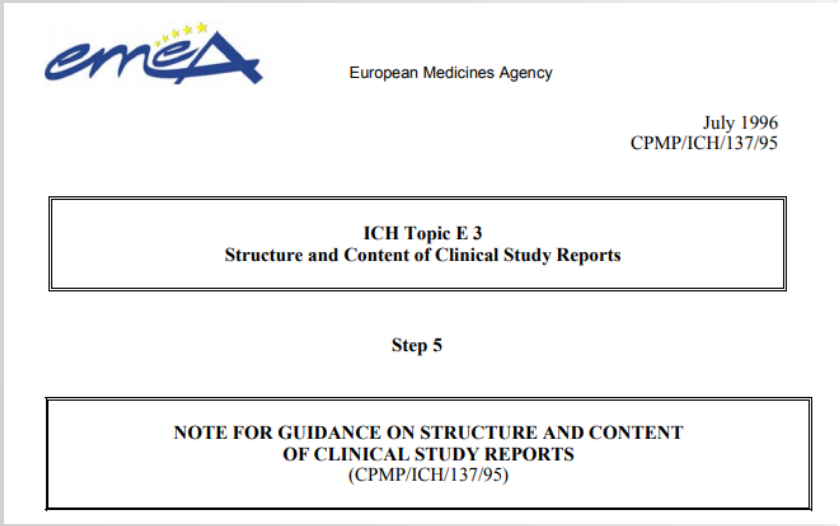
Publication writing

- How does publication writing differ for interventional trials and observational studies?

How to write a publication

1. Write the methods
2. Write the results
3. Write the introduction and the discussion

Interventional trial: clinical study report



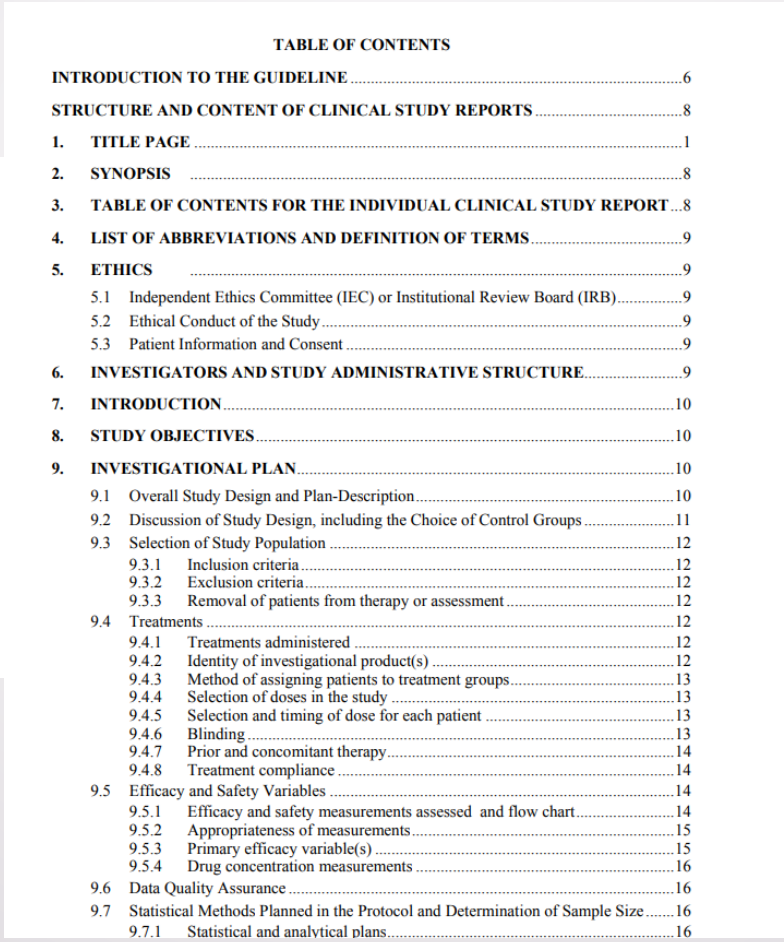
European Medicines Agency

July 1996
CPMP/ICH/137/95

ICH Topic E 3
Structure and Content of Clinical Study Reports

Step 5

NOTE FOR GUIDANCE ON STRUCTURE AND CONTENT OF CLINICAL STUDY REPORTS
(CPMP/ICH/137/95)



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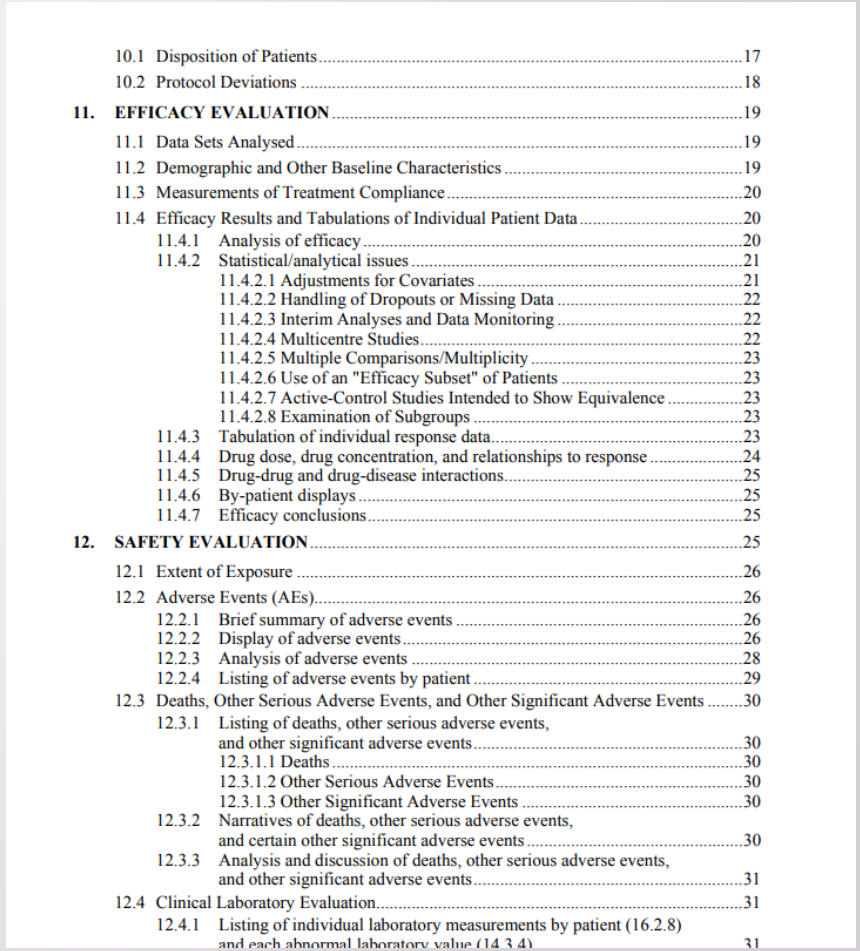


CONSORT methods

Methods		
Trial design	3a 3b	Description of trial design (such as parallel, factorial) including allocation ratio Import changes to methods after trial commencement (such as eligibility criteria), with reasons
Participants	4a 4b	Eligibility criteria for participants Setting and locations where the data were collected
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered
Outcomes	6a 6b	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed Any changes to trial outcomes after the trial commenced, with reasons

Trial design
3a
3b

Participants
4a
4b

Interventions
5

Outcomes
6a
6b

Methods

Design and participants

This was a randomized, double-blind, placebo-controlled study of the efficacy of TIV in prevention of vaccine-matched, culture-confirmed influenza (VMCCI) conducted in the 2005-2006 and 2006-2007 influenza seasons in the US. 3a

The original primary outcome measure defined by the study protocol was the average vaccine efficacy over two consecutive seasons in the prevention of culture-confirmed influenza. In correspondence following the 2005-2006 season, the FDA Center for Biologics Evaluation and Research noted that the season was marked by a significant frequency of circulation of influenza virus strains that were antigenically-drifted from those in the vaccine, and required that the protocol be modified to assess the average efficacy against VMCCI across both seasons as the primary measure of vaccine efficacy. 3b

Male and female volunteers aged 18 to 49 years inclusive were eligible to participate if they were clinically healthy, understood the study procedures, had access to telephone contact throughout study, and provided informed written consent. 4a In Season 1, eligible participants were enrolled at 37 centers, and in Season 2, eligible participants were enrolled at 44 centers. 4b

Exclusion criteria included: a significant acute or chronic, or medical or psychiatric illness requiring institution of new medical or surgical treatment, or a signifi-

CONSORT methods

Methods		
Randomisation Sequence generation	8a 8b	Method used to generate the random allocation sequence Type of randomisation; details of any restriction (such as blocking and block size)
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions
Blinding	11a 11b	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how
Statistical methods	12a 12b	Statistical methods used to compare groups for primary and secondary outcomes Methods for additional analyses, such as subgroup analyses and adjusted analyses

Inferential analysis

- Determines if there is a relationship between an intervention and an outcome
- Determines the strength of the relationship

The analysis of the primary end point was done using the closed-test principle. As a first step, a 2-sided Cochran-Mantel-Haenszel test adjusted for the variable pooled center was used for the micafungin dose groups on a significance level of $\alpha = 0.05$ to assess the difference between the dose groups. If the results allowed rejection of the null hypothesis of equality of the proportion p_x of patients with response (for H_0, $p_{50\,mg} = p_{100\,mg} = p_{150\,mg}$), then the groups were tested further with pairwise comparisons ($p_{50\,mg} = p_{100\,mg}$, $p_{50\,mg} = p_{150\,mg}$, $p_{100\,mg} = p_{150\,mg}$), each at a significance level of $\alpha = 0.05$, using a 2-sided Cochran-Mantel-Haenszel test adjusted for the variable pooled center.

The primary efficacy analysis was based on the average efficacy over Seasons 1 and 2 and assessed the null hypothesis that the average efficacy in the actively immunized group was ≤ 35%, against the alternative hypothesis that average efficacy was >35%. Average efficacy was defined as $1 - v(R_1R_2) \times 100$ where R_1 and R_2 were the relative risks of a given disease endpoint in Seasons 1 and 2, respectively. A one-sided 97.5% CI was constructed for the average efficacy, and the TIV efficacy target was to be established if the lower bound of the CI was >35%.

Descriptive analysis

- Describes the data: mean, median, standard deviation, confidence interval
  - Demographic data
  - Secondary outcomes
  - Safety data
- Occasionally primary outcome analysed descriptively

Solicited adverse events, unsolicited adverse events, and medically-attended adverse events were assessed in the reactogenicity and safety cohort. Serious adverse events and pIMDs were assessed in the total vaccinated cohort. We summarised reactogenicity and safety data with descriptive statistics and a two-sided 95% CI.

Analysis of Immunogenicity Endpoints

HI responses were analyzed descriptively, and associated 95% confidence intervals (CIs) were calculated. GMTs of H5N1 antibodies were calculated using the mean log-transformed titer.

Observational studies

Registry studies

National disease databases

Surveillance network studies

Medical records

Medical claims databases

Surveys

- **Rare genetic disorders**
- **Surgery**
- **Transplantation**
- **Infectious disease**

Observational studies

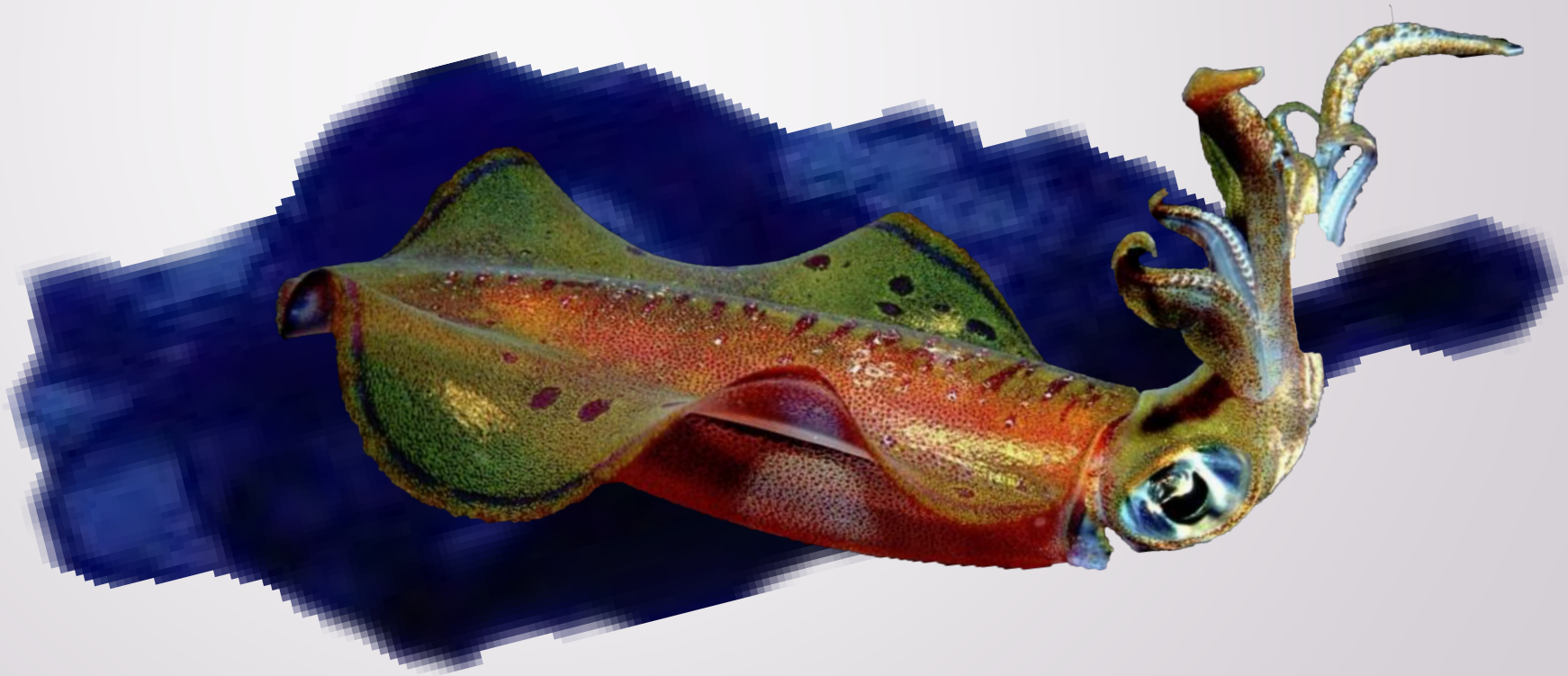
- **Varied/new concepts**
- **Mass of information**

Starting the publication

STROBE: Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objective	3	State specific objective, including any prespecified hypothesis

Don’t be a squid

Clear thoughts = clear writing



Behind the ink

- Researchers/modellers/statisticians have written the methods/report/publication

They see

A clear description of the study using all the special scientific words

You see

What was measured, how was it measured, and how was bias minimised?

Publication

1. Outcomes
2. Data sources
3. Statistics: confounders and adjusters

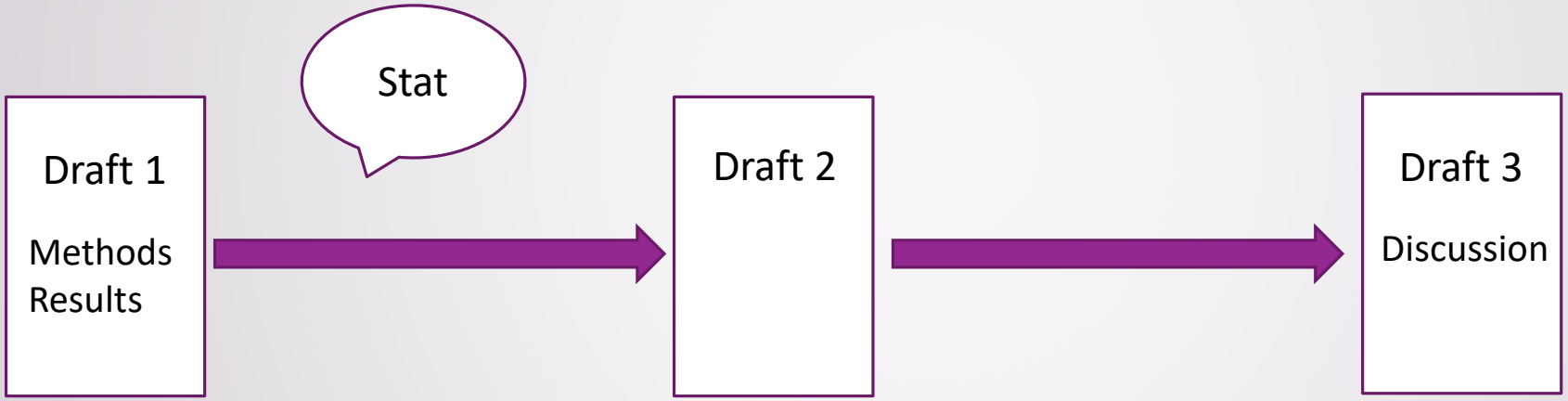
How was bias minimised?

STROBE: Methods		
Variables	7	Clearly define all outcomes, exposures, predictors**, potential confounders**, **and effect modifiers**. Give diagnostic criteria if applicable
Data sources/measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any **efforts to address potential sources of bias**
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which grouping were chosen and why
Statistical methods	12	(a) Describe all statistical methods, including those **used to control for confounding** (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) Cohort study If applicable, explain how loss to follow-up was addressed Case-control study — if applicable, explain how matching of cases and controls was addressed Cross-sectional study – If applicable, describe analytical methods taking into account of sampling strategy (e) **Describe any sensitivity analyses**

Research the statistical methods

- **Time series**
- **Immortal time bias**
- **Case-negative control**
- **Case-matched control**

Publication development



Writing the discussion

- **Interventional trial**
  - Presents the results in context of the literature
  - A paragraph on limitations describes the weaknesses of the study design
- **Observational trial**
  - Presents the results in context of potential confounders and how bias was addressed
  - Puts results in context of the literature

Thank you