Adverse Drug Reaction (ADR) screening in clinical trials

Pritibha Singh, Senior Quantitative Safety Scientist
Basel, Switzerland
November 29, 2016
Today’s talk at a glance

• How do we screen thousands of Adverse Events (AEs) reported in the case study to identify Adverse Drug Reactions (ADRs)?

• The Bradford Hill criteria to assess causal association between drug and AE (i.e. AE $\rightarrow$ ADR).

• The Double False Discovery Rate (DFDR) approach (Mehrotra & Adewale (2012)) applied to case study.
Lifecycle stage: Phase III

Pre-Clinical Phase  |  Phase I / PoC  |  Phase IIa  |  Phase IIb  |  Phase III  |  Approval  |  Post Launch

Early Development  |  Full Development  |  Launch

Case Study

- Pre-approval, Cardiovascular, Phase III program:
  - 1 large RCT, ~8000 patients
  - ~5 years planned follow-up
  - thousands of AEs to screen for ADR candidates
Adverse Drug Reaction (ADR) screening in Clinical Trials

AE → ADR

1\textsuperscript{st} dose administered to patient

last dose administered to patient

+ time after last dose

Treatment period

An adverse outcome reported in this period is an Adverse Event (AE*)

Bradford Hill Criteria

An Adverse Drug Reaction (ADR) is an AE/Serious AE (SAE) with at least reasonable possibility of a causal relationship between a medicinal product and the event ....: (FDA website)

*An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related (FDA website)
# AEs coded and summarized

## Large Phase III Clinical Trial

<table>
<thead>
<tr>
<th>Primary System Organ Class</th>
<th>Compound XX mg</th>
<th>Control XXX mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred term</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>N ~4000</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Subjects with at least one AE | ~3500 (~87.5) | ~3500 (~87.5) |

<table>
<thead>
<tr>
<th>Autoimmunity reactions</th>
<th>Total</th>
<th>Compound XX mg</th>
<th>Control XXX mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANKYLOSING SPONDYLITIS</td>
<td>~80</td>
<td>0</td>
<td>1 (0.0025)</td>
</tr>
<tr>
<td>AUTOIMMUNE HAEMOLYTIC ANAEMIA</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AUTOIMMUNE THYROIDITIS</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>BEHCGET'S SYNDROME</td>
<td>1 (0.0025)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CHRONIC GASTRITIS</td>
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Each PT would then be assessed for causality with drug via the Bradford Hill criteria.
Bradford Hill Criteria

Type of evidence
- Direct
  - Is there an association?

Mechanistic
- Biologically plausible
  - Biological mode of action can explain association

Parallel
- Consistency
  - Reproducibility of results, multiple studies or data sources report similar association

- Analogy
  - Evidence from another drug within the same class

Coherence
- Temporality
  - Exposure precedes AE or AE worsens post exposure

Specificity
- No other drug(s) could be causally related to AE

Biological gradient
- Dose-response (D-R)

Howick et al. (2009)
- Experiment
  - Experimental data provide strongest causal association evidence

- Strength
  - Large associations → more likely causal

- Context
  - Case Study
  - Key message & ?

Adverse Drug Reaction (ADR) screening in Clinical Trials

Thousands of PTs

Proposed ADR

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Proposed ADR

Context

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Key message & ?

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Proposed ADR

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Key message & ?
Case study: complex situation

Pre-Qualified ADR candidates
(Tier 1, Crowe et al. (2009))

- Designated Medical Events (DMEs) – AEs that require special attention regardless of statistical criteria used to prioritize safety reviews (EMA website)
- Risk Management Plan (RMP) – potential and identified risks for compound (EMA website)
- Core Data Sheet (CDS) – ADRs for our compound from already approved indications (ICH guideline E2C R2)

How to screen these remaining thousands of AEs (i.e. PTs) for ADRs?

Adverse Drug Reaction (ADR) screening in Clinical Trials

Source of ADR Candidate

All AEs (i.e. PTs) in this large Phase III clinical trial database
Selection of options

Question

How to screen thousands of AEs for ADRs?

Method

Individual case review

Useful for rare events

Double False Discovery Rate (DFDR)

Balance workload & false positive

Accounts for multiplicity

Issues addressed

Bayesian hierarchical models*

Accounts for correlations among AEs

Case Study Algorithm

*Berry & Berry (2004)
**DFDR multiplicity**

**Trial Design**
- Efficacy: Superiority/Equivalence/Non-inferiority of Investigational compound vs control
- May have ‘a priori’ safety concerns (RMP/CDS)

**During ADR screening phase**
- Large number of AEs → Multiplicity issue (PROTECT Symposium, 2015)
- Potential ADRs not identified at design stage, i.e. same database to generate and confirm multiple safety concerns
- Need to balance increased false positives (e.g. no adjustment i.e. p-value ≤ 0.05) and false negatives (e.g. overly stringent adjustment i.e. Bonferroni)
- Mehrotra and Adewale (2012) proposed the DFDR, which is a two-step process with two adjustments for multiplicity
DFDR: first adjustment (SOC)

SOC 1 – Hypothesis 1 (51 PTs)
Obtain unadjusted p-value 0.0003

SOC 2 – Hypothesis 2 (27 PTs)
Obtain unadjusted p-value 0.002

SOC 3 – Hypothesis 3 (42 PTs)
Obtain unadjusted p-value 0.012

SOC 4 – Hypothesis 4 (30 PTs)
Obtain unadjusted p-value 1

Obtain adjusted p-values (weighting and comparing exercise)
Flag SOCs → 2nd adjustment alpha=0.1

Adjusted p-values
SOC 1 = 0.000075
SOC 2 = 0.001
SOC 3 = 0.009
SOC 4 = 1

SOC 1, SOC 2, SOC 3 → 2nd adjustment

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DFDR: second adjustment (PT)

Create new family of hypotheses
n=120 hypotheses

51 PTs (SOC 1)

27 PTs (SOC 2)

42 PTs (SOC 3)

Obtain unadjusted p-value for each of the 120 hypotheses

Obtain adjusted p-values (weighting and comparing exercise)

Flag PTs → scientific evaluation alpha=0.1

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Case Study ADR screening strategy (Algorithm)

Exclude Pre-qualified ADR candidates

Tier 1 AE (Crowe et al.(2009))

Frequency too small to produce an unadjusted 1-sided p-value ≤ 0.1?

Tier 3 AE (Crowe et al.(2009))

Yes:
Individual case review of rare events and serious AEs

No:
Apply DFDR approach

Adjusted P-value > 0.1
No causality assessment

Tier 2 AE (Crowe et al.(2009))

Case study
Frequency of ≤ 4 in compound arm

Adjusted P-value ≤ 0.1
Causality assessment
Summary of ADR process

Algorithm

Exclude AEs and reduce dimension → Apply DFDR

Pre-qualified ADR candidates

Scientific evaluation based on medical and quantitative information

Bradford Hill Criteria

Proposed ADR

Confirm or reject ADR

Safety review board

Context
Case Study
Key message & ?
Key message

• DFDR is an elegant method to screen thousands of AEs to flag likely ADR candidates.

• DFDR balances workload and false positive signals, accounts for multiplicity, and needs to be combined with a method to evaluate rare events.

• The flagged potential ADR candidates proceed to scientific evaluation based on medical and quantitative information to assess causality.
Questions ...

Thank you
References


• FDA website: AE and ADR [ADR is referred to as suspected (drug) reaction] definition: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm362555.htm


• List of DME’s EMA website: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000587.jsp&mid=WC0b01ac0580727d1b
References


• PROTECT Symposium February 2015, Statistical signal detection in Clinical Trial data, Christiane Ahlers, Andreas Brueckner, Anngret Mallick, Nils Opitz, Vlasta Pinkston, Bruno Tran, Janet Scott, Harry Southworth, Bruno Tran, Lionel Van Holle, Nicola Wallis
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