Safeguarding public health

Overview of regulator's experience - Adaptive designs seen in Scientific Advice and by CHMP

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- **Do regulators like adaptive designs?**

- Regulators are heterogeneous!
  - though ‘Scientific Advice’ (SAWP / CHMP) and ‘Guidelines’ (EWP / CHMP) are agreed.

- ‘Adaptive designs’ are heterogeneous!

- Development programmes are heterogeneous!

- Experimental problems are heterogeneous!

- **Experience in confirmatory trials is very limited**
  - There have been very few **intentionally** ‘adaptive designs’ in regulatory submissions since an agreed definition of adaptive designs was reached - none at CHMP?
  - There have been trials submitted that would now be described as ‘adaptive’ but they were not analysed or assessed in this framework.

Experience at Scientific Advice Working Party

- We've stopped counting….!
- Approximately 15-20 requests for advice in the last two years.
- Indications include…anti-fungal, HIV, uveitis, anti-biotic, Type II diabetes, colorectal cancer, glioblastoma, multiple sclerosis, NSCLC …
- Vast majority were as confirmatory studies
- Majority were described as 'seamless' Phase II / III combinations incorporating dose-selection, sample-size re-estimation or both.
- Approximately 50% were single pivotal studies
- Some orphan products, but a minority.

Examples

•Orphan product in oncology. Randomised, patient-blind, single pivotal study.

•Phase III trial with OS as primary endpoint

•Interim analysis after every 20 patients to check progress

•Interim assessment (n=80) to judge effect size, assess efficacy and revise target sample size if required.

•Issues:
- Type I error not controlled
- Potential bias
- Development programme in a similar indication had exploratory trials and larger Phase III i.e. no 'gain' in information compared to other programmes
- Dissemination of interim data

• Conclusion: Major methodological concerns; proposal not endorsed.

Examples

•Cystic Fibrosis. Randomised, double-blind, placebo-controlled Phase II / III study.

•Single pivotal study, including interim analyses for early stopping (efficacy or futility)

•Potential re-assessment of sample size

•No sponsor involvement

•Type I error controlled

•Conclusions:
- No major concern relating to adaptive nature of the trial, except for potential inferences through knowledge of stopping rules.
- Cautions issued in line with the Reflection Paper.
- Concerns over totality of evidence likely to be available.
- Concerns over totality of evidence if trial is stopped early for efficacy

Examples

•Growth hormone.

•Large (n>1000) randomised, blinded, controlled trial.

•Time to event endpoint

•Proposal to adapt statistical analysis methodology from semi-parametric Cox proportional hazards model to parametric model using Weibull distribution if appropriate based on interim data

•Issues:
- What was the need?

•Conclusion:
- Proposal not endorsed.

Adaptations encountered (more than once!)

- Sample size re-assessment
  - Least controversial topic, if assessment is blinded
  - Compare with group sequential approach for efficiency – reduced regulatory concern?
- Randomisation ratio
  - Nervous of shift in population recruited
- Change or modification to primary endpoint / primary objective
  - Should reflect patient benefit, which is independent of interim data
  - Not really a candidate for adaptation
- Phase II / Phase III combinations
  - The correct design for a particular experiment?
  - How does the totality of evidence compare to separate trials?
  - Justifications based on resource, ethics but not science
  - Is the evidence really as good?
  - As single pivotal trials?
- Totality of evidence always critical.
- SAWP-recommended adaptations

• Predominately to discourage the adaptive designs that have been proposed to date, for reasons including …

- No acceptable rationale for using an adaptive design was presented – time and money to be saved, and ethical arguments, but no benefits in terms of **information** despite associated **risks**
- Totality of evidence likely to be inadequate (i.e. concern about the design of the programme).
- Critical methodological concerns inadequately addressed (bias, Type I error control)
- Concerns over dissemination of interim information (excessive sponsor involvement, 'open' discussions being held on interim data)
- Recruitment rate too slow
- Inadequate pre-specification of intention to adapt

•**In summary, only a minority of designs endorsed, with cautionary comments in line with the Reflection Paper. However, this is not due to a negative position *per se*.**

Concluding remarks

- Little experience with assessing completed trials.

- Some experience with proposals for adaptive designs

- Experience to date is disappointing…
  - methodological issues often inadequately addressed.
  - totality of development programme considered inadequate

- Regulators not adverse to adaptive designs as a matter of principle, but consider there to be **risks**.

- Reflection Paper should improve proposals by specifying minimal requirements and by focussing justifications.

Do regulators like adaptive designs?