INNOVATIVE CLINICAL TRIAL DESIGNS WELCOMED BY REGULATORS BUT WHAT ABOUT THE PAYERS?

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Leanne Larson MHA, Vice President & Global Head, Observational Research, PAREXEL International, Waltham, MA, USA
Andrew Walker PhD, Health Economist, Robertson Centre for Biostatistics, University of Glasgow, Glasgow
Detlev Parow MD, Head of Health Care Management, DAK Gesundheit, Hamburg, Germany

SPEAKERS AND AGENDA

Overview of innovative trial designs

Leanne Larson
VP & Global Head of Observational Research, PAREXEL Intl

Andrew Walker
Health Economist, Robertson Centre for Biostatistics

Detlev Parow
Head of Health Care Management, DAK Gesundheit

UK payer perspective on P&R issues for drugs utilizing these new clinical trial designs

DE payer perspective

Each panelist will speak for 10 minutes and this will be followed by a 15-minute panel discussion, and 15 minutes of Q&A from the audience.
THERE IS A LONG-STANDING DECLINE IN PHARMACEUTICAL R&D PRODUCTIVITY…

Eroom’s Law of Pharmaceutical R&D

*Inflation-adjusted trend in R&D efficiency*

... WHICH HAS DRIVEN NEW APPROACHES OF STUDY DESIGNS ...

Innovative clinical trial designs - overview

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<tbody>
<tr>
<td>1</td>
<td>Adaptive</td>
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<td>2</td>
<td>Umbrella</td>
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<tr>
<td>3</td>
<td>Basket</td>
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<td>Hybrid</td>
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These trial designs are not mutually exclusive – e.g. umbrella trials often have the flexibility to add/drop sub-trials (i.e. are also adaptive in nature)

... WHICH OFFER THE POTENTIAL TO MAKE DRUG DEVELOPMENT MORE EFFICIENT

Innovative clinical trial designs – key benefits and drawbacks

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<tbody>
<tr>
<td>Key potential benefits</td>
<td>Fewer patients receive ineffective treatments</td>
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<td>Development timelines &amp; costs</td>
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<tr>
<td>Key potential risks/drawbacks</td>
<td>Introduce operational and statistical biases</td>
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<td>Type 1 error rate</td>
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Adaptive trials

**Definition**

Prospectively planned opportunity
To modify the study design
Based on study outcome data

Multiple types of adaptive study design

- Adaptive randomization
- Group sequential
- Sample size re-estimation
- Drop-the-loser
- Adaptive dose-finding
- Biomarker-adaptive
- Adaptive treatment-switching
- Hypothesis-advantage
- Seamless phase II/III

Also multiple-adaptive designs combining several adaptive designs

Umbrella trials

**Definition**

Test multiple drugs on a single disease
e.g. each in a different biomarker-based cohort

Normally have the flexibility to add/drop arms

**Illustrative schematic of an umbrella trial**

Patients with disease
Biomarker profiling
Multiple sub-studies

Biomarker A+
Drug A vs. SoC

Biomarker B+
Drug B vs. SoC

Biomarker C+
Drug C vs. SoC

Biomarker negative
Drug D vs. SoC
THERE ARE SOME NOTABLE EXAMPLES OF THESE INNOVATIVE TRIAL DESIGNS IN PRACTICE…

STAMPEDE trial, an adaptive umbrella trial

**STAMPEDE began in 2007 as below**

- **Arm A**: HT alone (SoC)
- **Arm B**: HT + zoledronic acid
- **Arm C**: HT + docetaxel
- **Arm D**: HT + celecoxib
- **Arm E**: HT + zoledronic acid + docetaxel
- **Arm F**: HT + zoledronic acid + celecoxib

Randomised

Men starting hormone therapy (HT) for prostate cancer

In April 2017, the 9,000th patient was randomized

**Key trial adaptations / results**

<table>
<thead>
<tr>
<th>Date</th>
<th>Update</th>
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<tbody>
<tr>
<td>Apr 2011</td>
<td>Arms D &amp; F closed based on interim analysis results</td>
</tr>
<tr>
<td>Nov 2011</td>
<td>Arm G (HT+abiraterone) added</td>
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<tr>
<td>Jun 2013</td>
<td>Arm H (HT+RT) added (in M1 patients only)</td>
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<tr>
<td>Jul 2014</td>
<td>Arm J (HT +enzalutamide +abiratorone) added</td>
</tr>
<tr>
<td>May 2015</td>
<td>Arm C results – +docetaxel improves OS =&gt; new SoC</td>
</tr>
<tr>
<td>Apr 2016</td>
<td>Arm B&amp;E results – +zeledronic acid not improve OS</td>
</tr>
<tr>
<td>Sep 2016</td>
<td>Arm H closed based on interim analysis results</td>
</tr>
<tr>
<td>Sep 2016</td>
<td>Arm K (HT+metformin) added (in non-diabetics only)</td>
</tr>
<tr>
<td>Jul 2017</td>
<td>Arm G results +abiraterone improves OS</td>
</tr>
</tbody>
</table>

**…AND REGULATORS HAVE ISSUED GUIDANCE CAUTIOUSLY WELCOMING ADAPTIVE TRIAL DESIGNS…**

**FDA and EMA regulatory guidance on adaptive trials**

- **2007**: EMA
  - CHMP adopted the Reflection Paper on Methodological Issues in Confirmatory Clinical Trials Planned with an Adaptive Design

- **2010**: FDA
  - Draft Guidance for Industry – Adaptive Design Clinical Trials for Drugs and Biologics

Guidelines helped **clarify the regulatory position and concerns** on adaptive trials (which focussed primarily on the confirmatory phase)

Tone perceived as **cautiously welcoming** and guidance as generally received fairly positively by industry

Such guidance is key - otherwise the **risk & uncertainty** is too great
... HOWEVER PAYERS ARE INCREASINGLY BECOMING THE MAJOR HURDLES TO PATIENT ACCESS...

Evidentiary divergence – recent trends

Understanding the **payer perspectives** on these innovative trials designs and how these could impact reimbursement of new therapies will be key to understand.

UK HTA PERSPECTIVE

Andrew Walker
Andrew@salusalba.com
Yet another source of uncertainty.

Oh GOOD.

How do we respond?

TWO EXAMPLES TO CONSIDER

Example of BASKET
- Treat cancer patients with a common genetic mutation
- Multiple primary cancer sites
- Single arm clinical study
- N<100 in total
- For some primary cancer sites n=1
- ORR endpoint

Example of ADAPTIVE
- (Ultra) Orphan disease
- Two major manifestations (A,B)
- Start with mainly B (n=30)
- Expansion cohort mainly A (n=50)
- Emerging Q: are patients with BOTH A and B the best target?
HTA AGENCIES ALREADY COPE WITH CHANGE

Acknowledge HTA and Payers are DIFFERENT

All HTA decisions are made under uncertainty

HTA agencies already face:

- Licenses issued on the basis of conditional approval
- Surrogate endpoints that work for licensing but are of uncertain value
- Shifting attitude on role of equipoise/RCT – cope with increasing number of non-comparative studies
COPING WITH UNCERTAINTY AT NICE

‘Single arm’ clinical study only
Examples in classical HL (nivolumab), anaplastic (brentuximab) and Waldenstrom’s (ibrutinib)
Match to control cohort and / or new indirect comparison methods
All given some access

Managed access agreements
Nine examples of guidance issued or in final draft
Typically letting OS data collected in main study mature
Also collecting treatment duration in practice
Typically 2-4 years to report

Interpretation: even high levels of uncertainty can be acceptable with the right techniques and tools

But will this apply to innovative study designs?
Does HTA recognise the need for AP design?

At director level, maybe yes
At committee member level, probably no

Why?
Systematic attempt to lower evidence standards
Early access for commercial reasons
A way for companies to have their cake and eat it
Shift risks and R&D costs onto the taxpayer
ARE SOME ADAPTATIONS LESS UNACCEPTABLE?

Candidates:

Expansion cohort? Yes, HTA considers patients who match license

Dose changes? Yes, same logic, match the license

Primary endpoint? Hmm, could be seen as a weakness, may depend on reason for the change e.g. fell short of expectations

Explanation of need for adaptation and perceived motive will matter

MORE EFFICIENT DESIGN?

• Unintended consequences: lower R&D costs, lower prices

• Might be conditional HTA acceptance but lower price expected and will this ever be restored? Plus delay in negotiating

• Key issue: who selects adaptations and on what basis – in pursuit of ‘science’ or ‘profit’?

• Incentivise speculative behaviour – try it in very broad population, can always change it
I predict UK HTA will start from the license

and will be quite pragmatic in considering all the evidence

but there will be a price to pay in terms of willingness to accept a higher and less certain cost per QALY

ADVICE FOR COMPANY

- Early engagement with HTA organisations
- See things from their point-of-view, at least when you rehearse
- Be warned this involves listening as well as explaining
- Might hear things are no as simple as internal company logic suggests
- There are pragmatic attitudes out there, but not at any price
- Expose the company to realistic external attitudes early & often
Innovative Clinical Trial Designs
Welcomed by Regulators but what about the Payers?

Glasgow, November 8th 2017
Dr. Detlev Parow, MBA, DAK-G

Disclaimer: Statements and opinions expressed in this presentation are sole views of the presenter. They are not necessarily the opinion or position of DAK-Gesundheit and could not be regarded as an official statement.

DAK-Gesundheit: Germany's longest-standing and third-largest SHI company is a quality leader

- Germany's third largest nationwide statutory health insurance company
- 5.9 million insured, (approx. 8.0% market share)
- Annual expenditures: EUR 20.0 billion in health insurance
- **Drug spending:** EUR 3.8 billion (approx. 11% of GKV drug costs)
- MedTech spending: approx. EUR 2.1 billion (estimate based on DAK-G, BMG and MVMed Data)
The good old ancient times:
Drugs were cheap, effective and cure instantaneously

The long term healthcare goals are clear:
Patients need access to healthcare and medicines

Rational use of medicines

Sustainable financing

Access to medicines

Affordable prices

Drug approval:
FDA / EMA
Focus: safety + effectiveness

HTA Germany:
GBA / IQWIG
Focus: additional benefit to SoC

Reliable health and supply system

Source: WHO, The World Medicines Situation, 2004, modified by Ian Talmage, adapted by me
AMNOG was designed to prevent the problem of pushing the healthcare system beyond its financial limits.

<table>
<thead>
<tr>
<th>Manufacturer / GBA / IQWIG</th>
<th>Manufacturer / GKV-SpV</th>
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<tbody>
<tr>
<td>Market Introduction</td>
<td>Market Introduction</td>
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<tr>
<td>Benefit Assessment (Publication)</td>
<td>Benefit Assessment (Decision)</td>
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<td>Federal Joint Committee</td>
<td>Federal Joint Committee</td>
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<tr>
<td>Reference price (Max. for SHI reimbursement)</td>
<td>Discount (on manufacturer's price)</td>
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<tr>
<td>No added benefit</td>
<td>Discount (on manufacturer's price)</td>
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<td>No access restrictions, no forth hurdle</td>
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<td>6 months</td>
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<td>12 months</td>
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The GBA's / IQWIG's AMNOG-assessment is based on active pharmaceutical compound, indication and comparator:

- One active pharmaceutical compound (or combination) / one indication
- Appropriate comparator (SoC / maybe several / maybe different)
- Differentiation of study population in several subgroups
- Different aspects of the assessment
  - Mortality
  - Morbidity
  - Side-effects / adverse effects / drug safety
  - Quality of life
- Objective: to define the additional benefit compared to SoC
- Different levels of additional benefit
  - Less, no, not quantifiable, minor, considerable, major additional benefit
- Different evidence categories
  - proof, indication, hint, based upon the number and characteristics of studies provided
The schematic diagram of AMNOG is complex:
AMNOG reality is even more complex

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<tr>
<th>Pharmaceutical compound</th>
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<th>PC 2 (+)</th>
<th>PC n</th>
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<td>X (10,000)</td>
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<td>Ass. 1</td>
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<td>6 levels: major additional benefit – less beneficial</td>
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<td>Probabilities: proof, hint, indication</td>
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<td>Ass. 2</td>
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The Institute for Quality and Efficiency in Health Care favours RCTs for the assessment of drug interventions

Randomization is the best currently available instrument to minimize bias. In RCTs the fundamental requirements for a proof of causality are given. Other types of studies as RCTs are not usually suitable for a proof of causality.

The randomized controlled trial is the gold standard in the assessment of drug interventions. Usually RCTs are possible and practically feasible. Only in exceptional cases non-randomized intervention studies or observational studies may be taken into account.
The Institute for Quality and Efficiency in Health Care favours RCTs for the assessment of drug interventions

Only randomized controlled trials, based on the random assignment of subjects, sufficiently ensure that known and unknown patient characteristics that interfere with or distort a fair comparison of two or more medical interventions are equally distributed. Even with a high degree of innovation dynamics, evaluations of the benefits and harms of medical methods and products can be based on robust evidence for the protection of patients.


Innovative clinical trial designs – overview: How does this fit to GBA / IQWiG scientific approach

1. Adaptive
   Yes: if modifications are already defined in study design

2. Umbrella
   Yes: as long as each arm is sufficiently powered vs. SoC

3. Basket
   Yes: as long as each indication is sufficiently powered vs. SoC

4. Hybrid
   No: Integration of prospective and retrospective data is no RCT

Stolen from: Leanne Larson, VP & WW Head, Real-world Evidence Strategy, PAREXEL Intl
Thank you for your attention.
Don’t hesitate – let’s talk about it!

Innovative Clinical Trial Designs, Glasgow, 2017-11-08