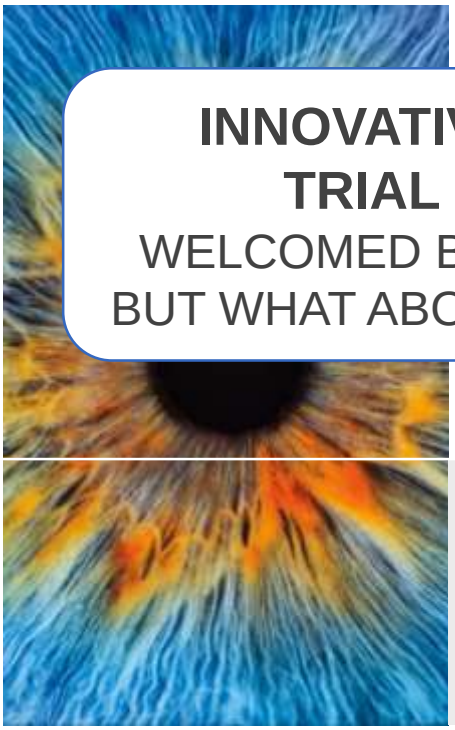

INNOVATIVE CLINICAL TRIAL DESIGNS

WELCOMED BY REGULATORS BUT WHAT ABOUT THE PAYERS?

November 2017
ISPOR Glasgow

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

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SPEAKERS AND AGENDA

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

Overview of innovative trial designs

Andrew Walker
Health Economist, Robertson Centre for Biostatistics

Detlev Parow
Head of Health Care Management, DAK Gesundheit

UK payer perspective

DE payer perspective

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

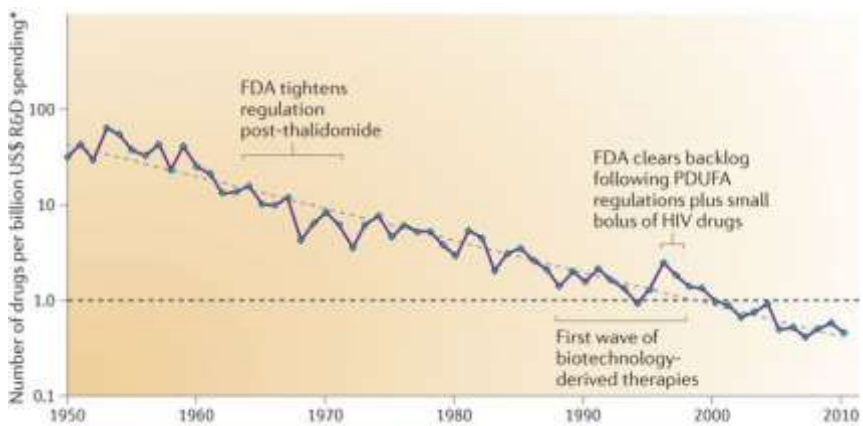
Each panelist will speak for 10 minutes and this will be followed by a 15-minute panel discussion, and 15 minutes of Q&A from the audience

INNOVATIVE CLINICAL TRIAL DESIGNS

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[1]



SOURCE: [1]Scannell et al. Nat Rev Drug Discov. 2012 Mar 1;11(3):191-200..

… WHICH HAS DRIVEN NEW APPROACHES OF STUDY DESIGNS…

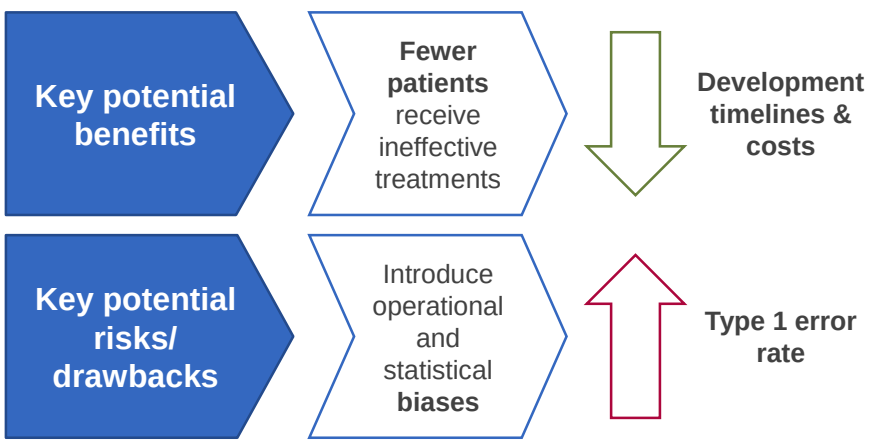
Innovative clinical trial designs - overview

1	**Adaptive**	**Allows modifications to the trial** after its initiation
2	**Umbrella**	Test **multiple drugs** on a single disease
3	**Basket**	Test a single drug across **multiple diseases**
4	**Hybrid**	**Integrate** prospective and **retrospective** data

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



ADAPTIVE TRIALS ARE POTENTIALLY THE MOST WELL RECOGNISED OF THESE INNOVATIVE TRIALS…

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

… ALONGSIDE UMBRELLA TRIALS WHICH ALLOW THE TESTING OF MULTIPLE DRUGS FOR A DISEASE

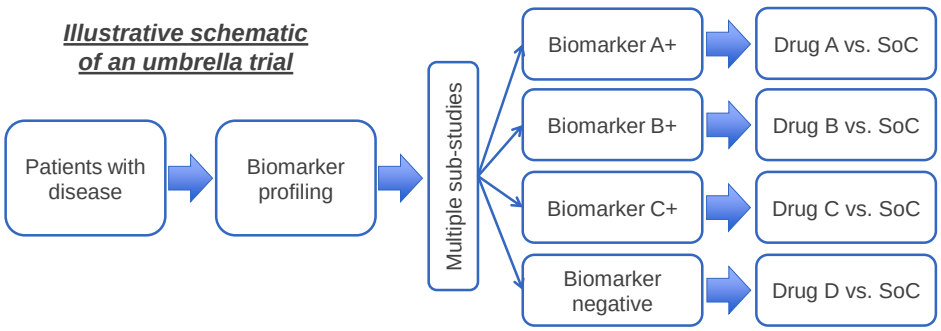
Umbrella trials

Definition

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

+ an adaptive element → Normally have the **flexibility to add/drop arms**

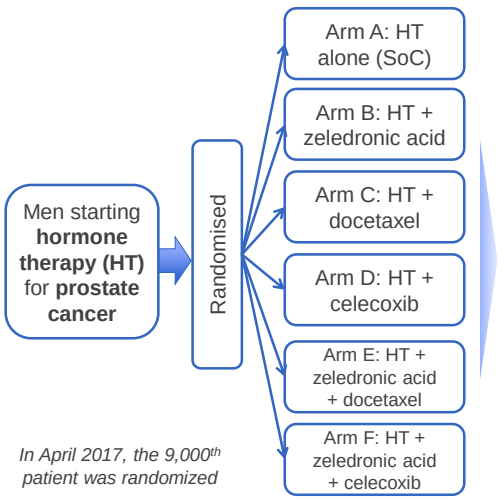
Illustrative schematic of an umbrella trial



THERE ARE SOME NOTABLE EXAMPLES OF THESE INNOVATIVE TRIAL DESIGNS IN PRACTICE…

STAMPEDE trial, an adaptive umbrella trial

STAMPEDE began in 2007 as below



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

Key trial adaptations / results

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

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

FDA and EMA regulatory guidance on adaptive trials

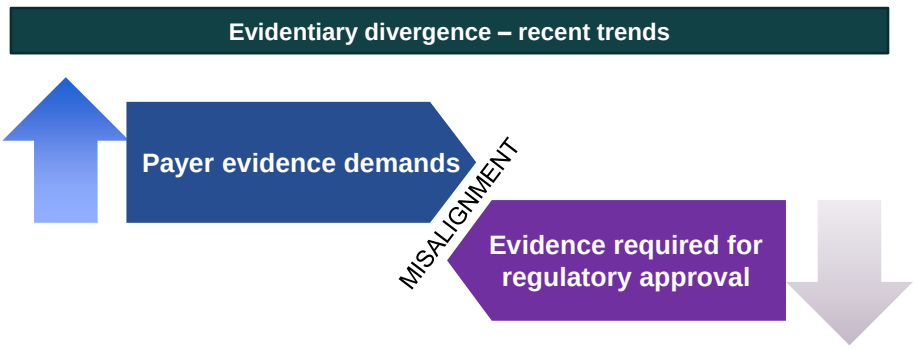
2007	EMA	CHMP adopted the Reflection Paper on Methodological Issues in Confirmatory Clinical Trials Planned with an Adaptive Design
2010	FDA	Draft Guidance for Industry – Adaptive Design Clinical Trials for Drugs and Biologics

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…



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

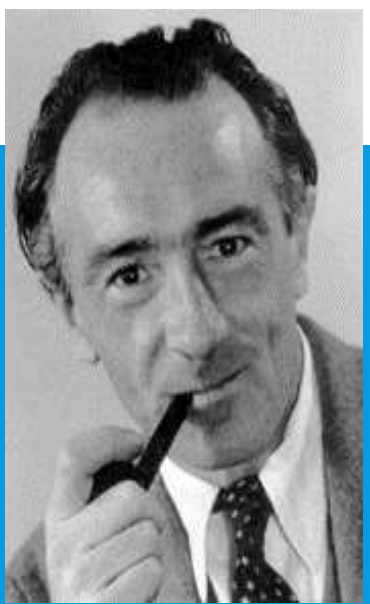
All HTA decisions are made under uncertainty

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?

Health Technology Assessment in the Context of Adaptive Pathways for Medicines in Europe: Challenges and Opportunities

JC Bouvy[1], P Jonsson[1], C Longson[1], N Crabb[1] and S Garner[1]

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?

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.

Glasgow, November 8th 2017

Dr. Detlev Parow, MBA, DAK-G

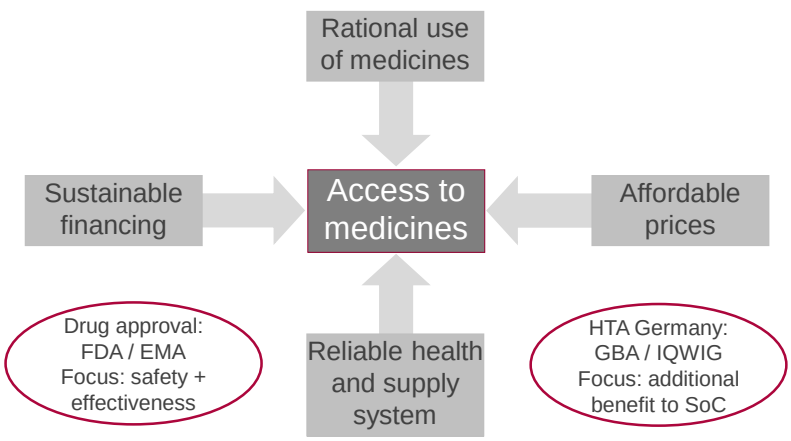
DAK-Gesundheit: Germany's longest-standing and third-largest SHI company is a quality leader

- 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)

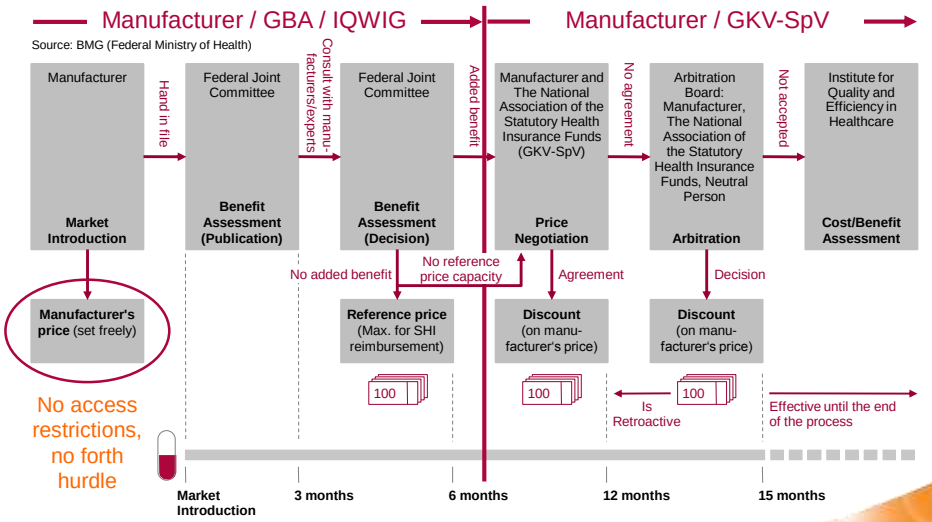
The good old ancient times:
Drugs were cheap, effective and cure instantaneously

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



Source: WHO, The World Medicines Situation, 2004, modified by Ian Talmage, adapted by me

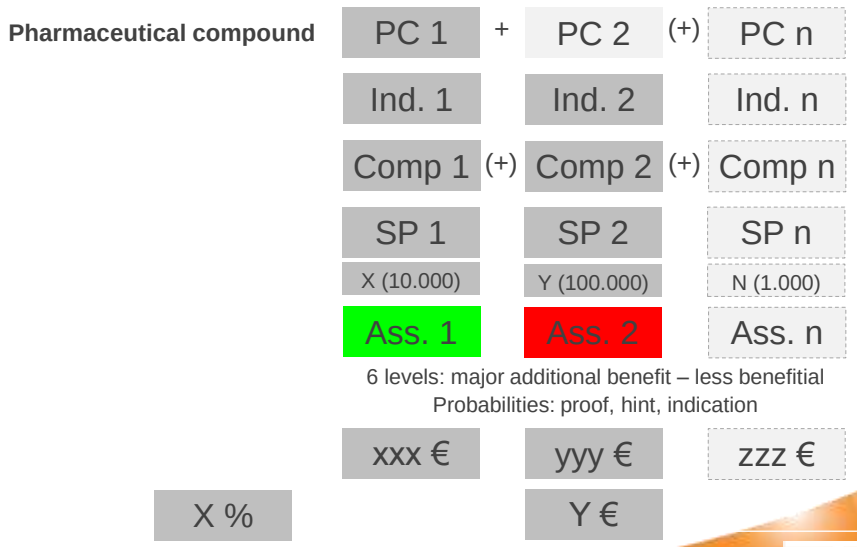
AMNOG was designed to prevent the problem of pushing the healthcare system beyond its financial limits



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 assessement
  - 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



The Institute for Quality and Efficiency in Health Care favours RCTs for the assessment of drug interventions

IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Institute for Quality and Efficiency in Health Care

Institut für Qualität und

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.

Allgemeine Methoden 5.0

General Methods 5.0 (German version only)

published 10th July 2017

The Institute for Quality and Efficiency in Health Care favours RCTs for the assessment of drug interventions

IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Institute for Quality and Efficiency in Health Care

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.

Lange S, Sauerland S, Lauterberg J, Windeler J:
The range and scientific value of randomized trials—part 24 of a series on evaluation of scientific publications. Dtsch Arztebl Int 2017; 114: 635–40.
DOI: 10.3238/arztebl.2017.0635

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 – lets talk about it!
Innovative Clinical Trial Designs, Glasgow, 2017-11-08