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Adaptive Pathways & Conditional Approval

A critical appraisal

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Overview

1. Adaptive Pathways
2. Conditional Approval
3. Real World Data
4. Critique and Words of Caution – Case Reports

Part 1:
Adaptive Pathways

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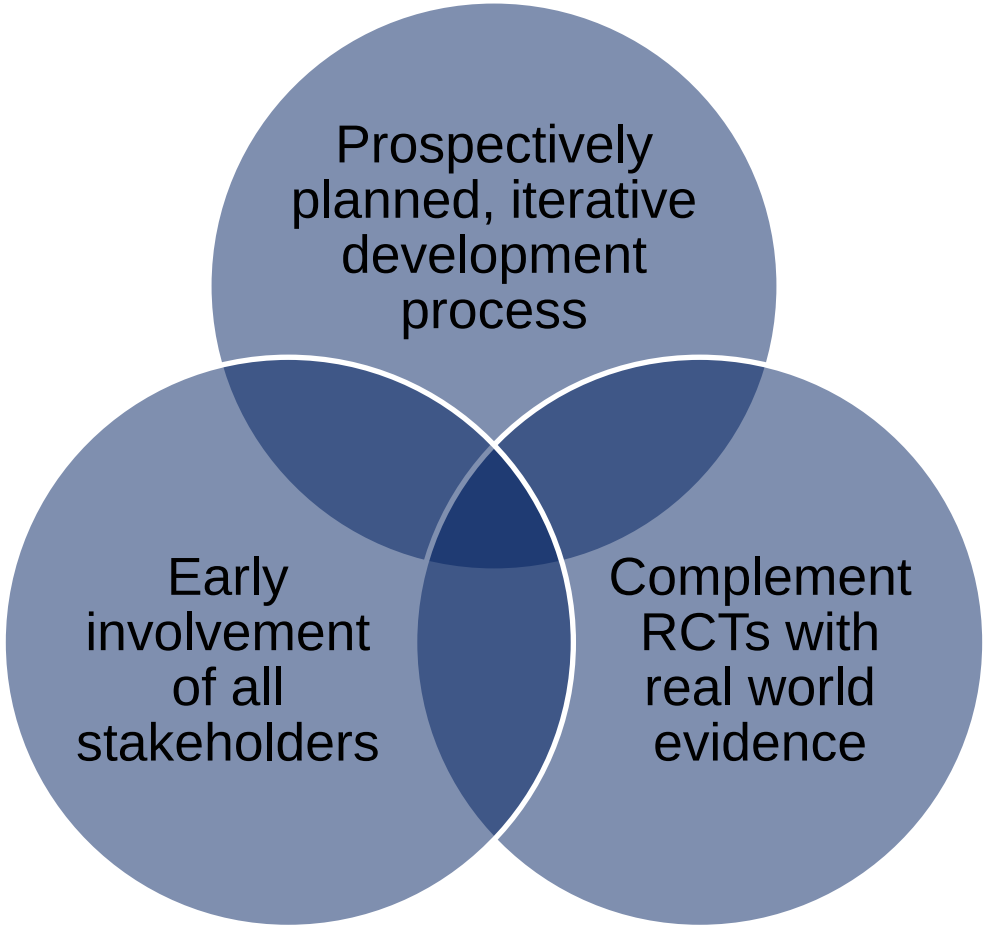
Adaptive Pathways



EMA – Adaptive Pathways

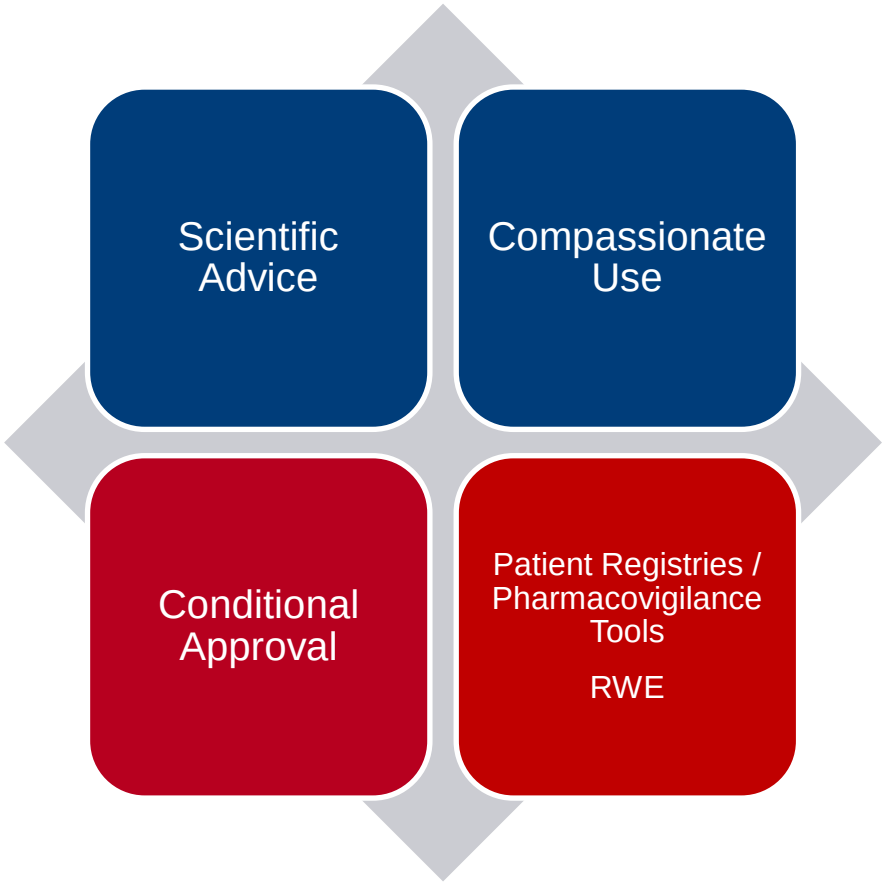
- Improves timely access for patients to new medicines
- Allows for early and progressive patient access to a medicine

- Applies primarily to areas with “high medical need”

- Adaptive Pathways are based on the following principles:
  - Iterative development
    - Approval in stages from restricted to wider population
    - Conditional approval based on early data / surrogate endpoints
  - Gathering evidence through real-life use
  - Early involvement of patients and HTAs

- Patients / patient representatives (especially in rare diseases) want fast access to save and efficacious drugs

Adaptive Pathways are based on existing tools



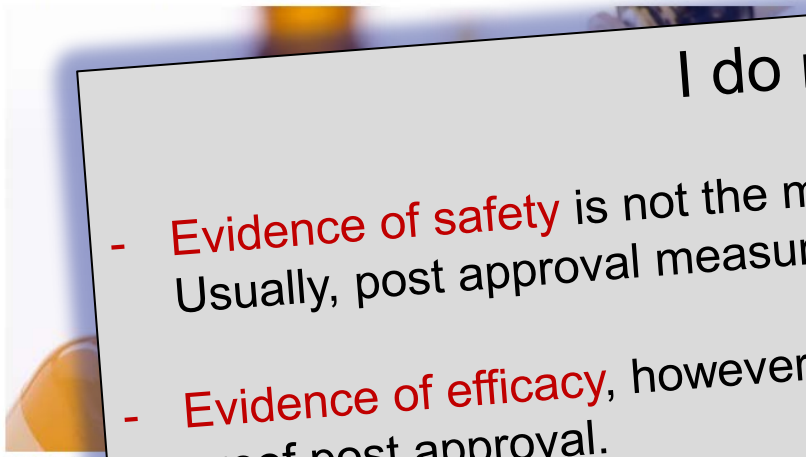
- Not intended to change the standards of evaluation of MAA dossiers

Critique on fast approval schemes

IQWIG-VIZE ZU SCHNELLEN ZULASSUNGEN

EMA darf Zulassungs-Konsens nicht aufkündigen

STUTTGART - 05.09.2016, 09:00 UHR



Wie schnell dü
Absenkung der

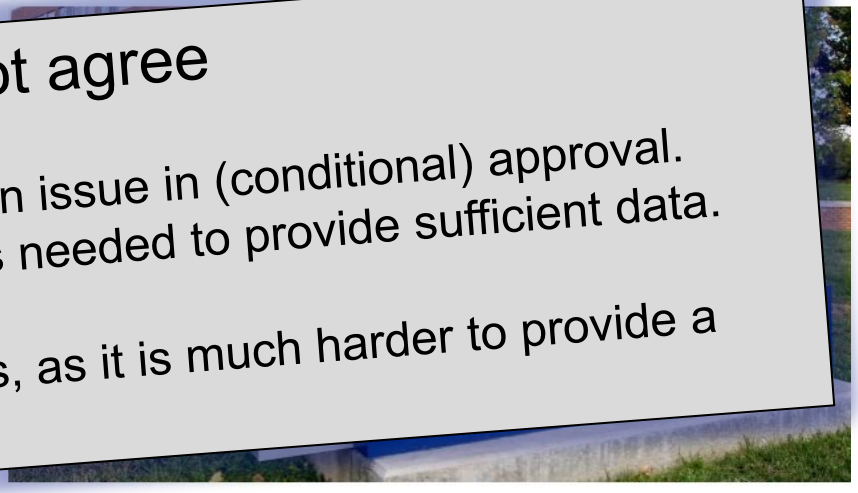
Wenn die Arzneimittelbehörden mit Konzepten wie „Adaptive Pathways" schnelle Zulassungen zum Regelfall machen wollen, gefährden sie die Sicherheit: IQWiG-Vize Stefan Lange kritisiert im Interview mit DAZ.online die Pläne der EMA scharf. Die Standards, die nach dem Contergan-Skandal aufgestellt wurden, dürften nur aufgrund eines politischen Prozesses geändert werden.

Source:
https://www.deutsche-apotheker-zeitung.de/news/artikel/2016/09/05/ema-darf-zulassungs-konsens-nicht-aufkuendigen

NACH ÄUSSERUNGEN EINES TRUMP-KANDIDATEN

FDA wehrt sich gegen Aufweichung von Standards

STUTTGART - 24.01.2017, 07:00 UHR



Arzneimittelbehörden stehen oft in der Kritik, neue Arzneimittel zu langsam zuzulassen. Nun legt die US-amerikanische FDA Material vor, das zeigt, warum sich Phase-3-Studien lohnen. Dies könnte sich gegen ihren zukünftigen Chef richten, den US-Präsident Donald Trump ins Spiel gebracht hatte: Der Investmentbanker Jim O'Neill hatte vorgeschlagen, auf Wirksamkeitstests zu verzichten.

Source:
https://www.deutsche-apotheker-zeitung.de/news/artikel/2017/01/24/fda-wehrt-sich-gegen-aufweichung-von-standards

I do not agree

- Evidence of safety is not the main issue in (conditional) approval. Usually, post approval measures needed to provide sufficient data.
- Evidence of efficacy, however, is, as it is much harder to provide a proof post approval.

EMA Pilot: Adaptive Pathways

- From March 2014 to August 2016
- 62 applications
  - 18 proposals selected for f2f meetings
    - 6 applicants received parallel advice (EMA / HTA)
    - 1 applicant received EMA advice

Source: Final report on the adaptive pathways pilot EMA/276376/2016

Issues identified for further reflection

- Involvement of patients and healthcare professionals
  - Further input by patients and healthcare professionals needed.
  - What is unmet need?
    - medical need?
    - public health need?
    - healthcare cost savings?
- Post-authorisation data gathering plans
  - Sound methods needed for real-world data
- Involvement of payers
  - Payers (i.e., bodies responsible for pricing on the basis of HTA assessment) were not part of the pilot

Source: Final report on the adaptive pathways pilot EMA/276376/2016

Conclusion on Adaptive Pathways

- ✓ No (real) results from pilot
- ✓ A lot of critique from stakeholders (HTAs, public, …)

- ➢ However, we can have a look at the applied tools which are interesting in their own right:
  - ➢ Conditional Approval
  - ➢ Real World Data

Part 2:
Conditional Approval

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CMA Conditional Marketing Authorisation

How early access to medicines has helped patients from 2006 to 2016

What it is

- an EU early access route for medicines
- for medicines that fulfil an unmet medical need
- only granted if the benefit of immediate availability for patients is greater than the risk of less comprehensive data than normally required
- valid for a year; can be renewed annually
- comprehensive data is generated post-authorisation, to agreed timelines

Scope includes

- medicines to target seriously debilitating or life-threatening diseases
- medicines to fight public health threats in emergency situations (e.g. a pandemic)
- medicines to treat rare diseases

30 CMAs

- 24 Target debilitating or life-threatening conditions
- 14 Are orphan medicines
- 3 Address emergency situations linked to a public health threat

By therapeutic area

17 Oncology

9 Infectious diseases

3 Neurology

1 Ophthalmology

Source: EMA Website on CMA, 10 year report;
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000925.jsp

107 post-authorisation obligations

(of these, 57 obligations were fulfilled before June 2016)

Categories of specific obligations imposed to companies

78	Final results from clinical studies or pool of studies
9	Interim results of a clinical trial
8	Additional analysis
3	Quality data
9	Other measures

How timely was the submission of specific obligation results?

33	Due date +/- 1 month
15	Early (1-6 months)
4	Early (6-12 months)
1	>1 year early
2	Late (1-6 months)
2	Late (6-12 months)

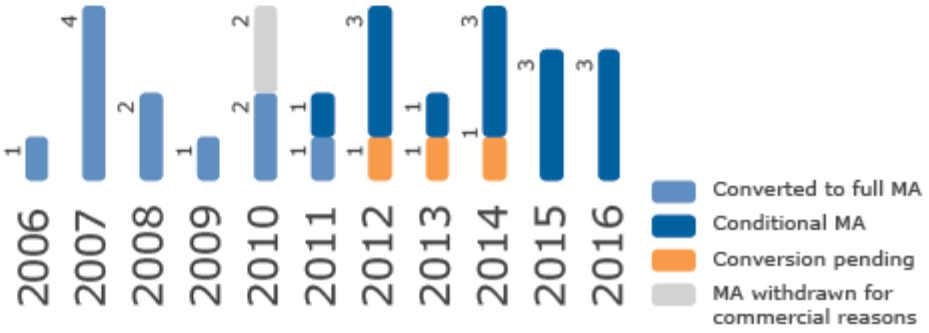
>90% of completed specific obligations did not have major changes to their scope

≈70% of specific obligations were completed within specified timelines

By year

EMA's Committee for Medicinal Products for Human Use (CHMP) reviews all data collected annually to decide about a further renewal of the CMA or its conversion into a standard marketing authorisation.

On average, a CMA is converted into a standard marketing authorisation **within 4 years.**



Source: EMA Website on CMA, 10 year report;
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000925.jsp

Conditional Approval

Why is conditional approval a double-edged sword?

- Benefit:
  - Fast(er) market access
    - Beneficial for applicant/MAH?
    - Beneficial for patients?
    - Beneficial for payers?
    - Beneficial for doctors?
- Risks:
  - Typically based on Phase II data and/or uncontrolled studies or otherwise immature data
  - Preliminary data (w.r.t. follow up)
  - (Potentially) only surrogate endpoint(s)
  - Difficulty to obtain relevant data after (conditional) approval
    - Randomised studies still possible? (pragmatic trials?)
    - Proper results from observational studies or registers, especially w.r.t. efficacy?

Statistical Issues of Conditional Approval

- Interim Analyses (for MAA)
  - Sufficient evidence (see above)?
  - Study integrity?

- Single-arm trials / historical controls
  - Choice of controls? (matching?)
  - Same inclusion criteria?
  - Same treatment / measurement standards?
  - …

Consequences:

- Biased estimate of treatment effect (B/R? SmPC?)
- Inconclusive results (positive B/R?)

Part 3:
Real World Data

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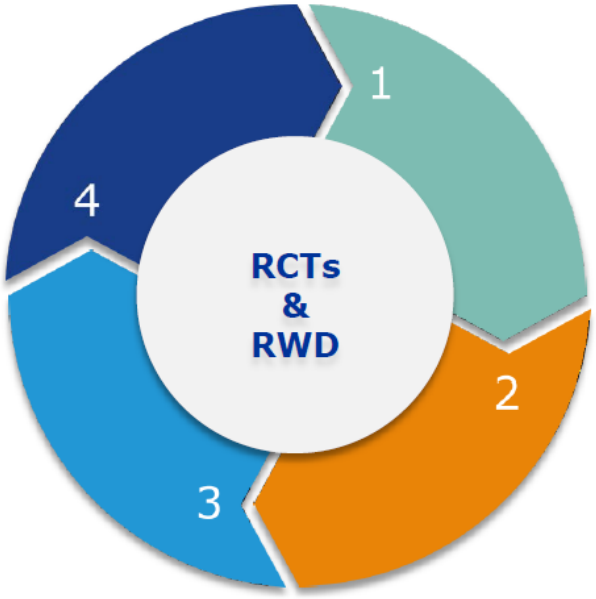
Randomised Controlled Trials (RCTs) and Real World Data (RWD)



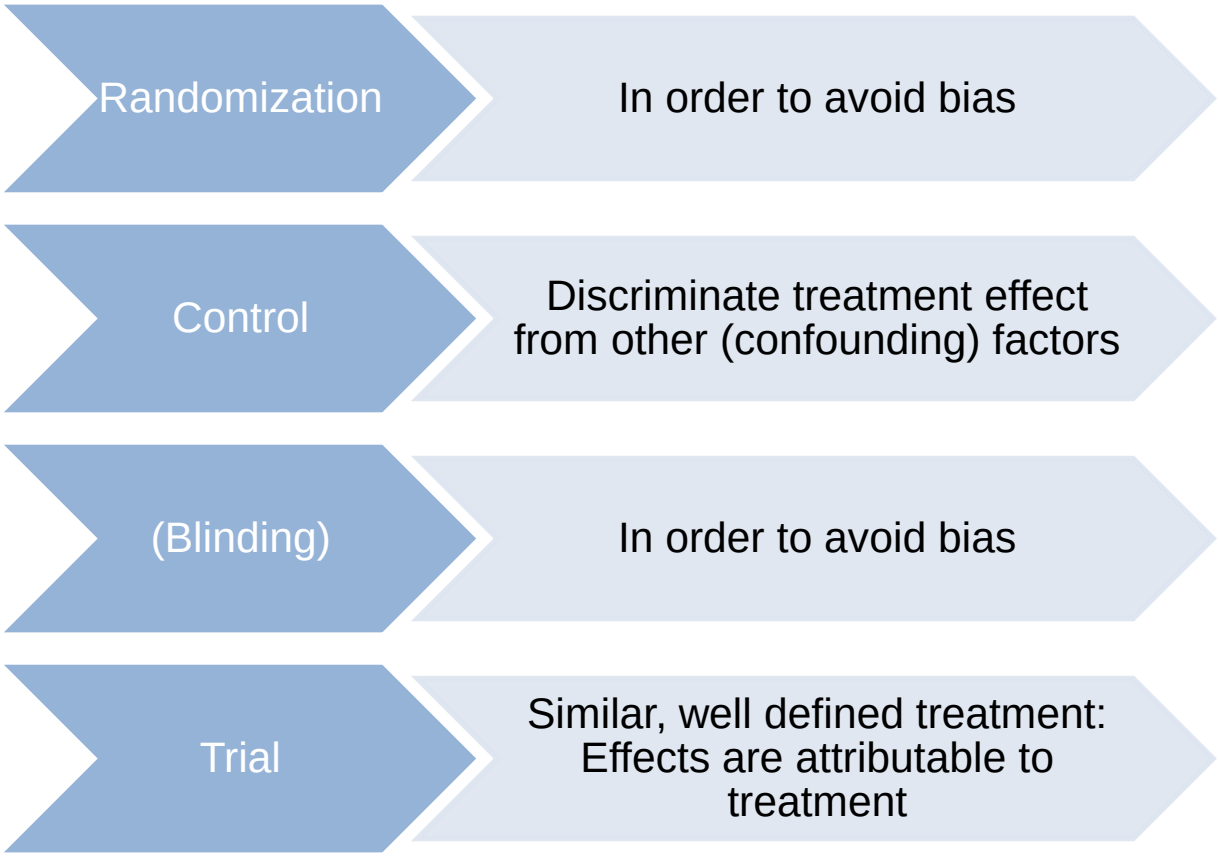
1. RCTs are the methodology with the highest internal validity (≠ 'gold standard', not black & white)
2. For efficient increase of knowledge of benefits and risks: embrace the full evidence spectrum (RCTs, pragmatic trials, observational studies)
3. RWD complements rather than replaces RCTs. The right study type for the right question – where feasible
4. Pre and post-licensing evidence generation are not two different lives, it's one continuous life

8

Source: Hans-Georg Eichler (2016), Adaptive Pathways: concept and critical issues [Presentation] http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2016/12/WC500218594.pdf

Randomized Controlled Trials

Why do we (still) (have to) rely on RCTs?



Possible Exceptions to RCTs

- Self-evident causality / extreme effects
  - E.g. Avexis: treatment of spinal muscular atrophy (Type 1) [PEI Scientific Advice]

- More pragmatic reason:
  - (Ultra) rare diseases → Feasibility? Ethical issues?

Real World Evidence

- Recent reflections from FDA
  (08.12.2016)

The NEW ENGLAND JOURNAL of MEDICINE

SOUNDING BOARD

Real-World Evidence — What Is It and What Can It Tell Us?

Rachel E. Sherman, M.D., M.P.H., Steven A. Anderson, Ph.D., M.P.P., Gerald J. Dal Pan, M.D., M.H.S., Gerry W. Gray, Ph.D., Thomas Gross, M.D., M.P.H., Nina L. Hunter, Ph.D., Lisa LaVange, Ph.D., Danica Marinac-Dabic, M.D., Ph.D., Peter W. Marks, M.D., Ph.D., Melissa A. Robb, B.S.N., M.S., Jeffrey Shuren, M.D., J.D., Robert Temple, M.D., Janet Woodcock, M.D., Lilly Q. Yue, Ph.D., and Robert M. Califf, M.D.

So, what is it?

1. No clear definition.
2. No clear „application“. (I will focus on efficacy in the context of market authorization)
3. Often refers to information on health care that is derived from multiple sources outside typical clinical research settings, including
   - electronic health records (EHRs),
   - claims and billing data,
   - product and disease registries, and
   - data gathered through personal devices and health applications.

   Difficult in GER due to data protection laws

   → „Big Data“
4. Not opposed to randomized trials!
5. Goals are for example
   - Choice of treatment
   - Personalised / precision medicine
   - Evidence of effectiveness in real live setting

Pragmatic Clinical Trials for Real World Evidence

Uncertain quality and provenance of data might hamper usefulness. Hence, carefully set up study designs and analyses are needed:

Article

CLINICAL TRIALS

Pragmatic clinical trials: Emerging challenges and new roles for statisticians

Clinical Trials
2016, Vol. 13(5) 471–477

DOI: 10.1177/1740774516656944
ctj.sagepub.com
SAGE

Robert M Califf
Former Commissioner of the FDA

"The informed guess of an expert is better than nothing—but empirical proof that a given treatment has a favourable balance of benefit to risk is much better still."

Pragmatic Clinical Trials

- Less separation from standard patients regarding
  - inclusion criteria,
  - treatment modalities,
  - data collection,
  - …
- Randomized or cluster randomized (i.e., randomly assign bigger entities such as centers to treatment arms) pragmatic trials possible and useful
- Given careful decision on study design (QBD), results might be better to generalize

- Further methodological problems remain (to a certain extend):
  - Bias, confounding, missing values, …

There is still a lot to do…

Article

CLINICAL TRIALS

Clinical Trials
2016, Vol. 13(5) 471–477

DOI: 10.1177/1740774516656944
ctj.sagepub.com
SAGE

Pragmatic clinical trials: Emerging challenges and new roles for statisticians

Robert M Califf

Abstract

Patients, clinicians, and policymakers alike need access to high-quality scientific evidence in order to make informed choices about health and healthcare, but the current national clinical trials enterprise is not yet optimally configured for the efficient creation and dissemination of such evidence. However, new technologies and methods hold significant potential for accelerating the rate at which we are able to translate raw findings gathered from both patient care and clinical research into actionable knowledge. We are now entering a period in which the quantitative sciences are emerging as the critical disciplines for advancing knowledge about health and healthcare, and statisticians will increasingly serve as critical mediators in transforming data into evidence. In this new, data-centric era, biostatisticians not only need to be expert at analyzing data but should also be involved directly in diverse efforts, including the review and analysis of research portfolios in order to optimize the relevance of research questions, the use of "quality by design" principles to improve reliability and validity of each individual trial, and the mining of aggregate knowledge derived from the clinical research enterprise as a whole. In order to meet these challenges, it is imperative that we (1) nurture and build the biostatistical workforce, (2) develop a deeper understanding of the biological and clinical context among statisticians, (3) facilitate collaboration among biostatisticians and other members of the clinical trials enterprise, (4) focus on communication skills in training and education programs, and (5) enhance the quantitative capacity of the research and clinical practice worlds.

Part 4:
Critique and Words of Caution
- Case Reports -

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FDA Case Study

- To better understand the nature of the evidence obtained from many Phase II trials and the contributions of Phase III trials of drugs, vaccines and medical devices, FDA studied 22 recent cases in which promising Phase II clinical trial results were not confirmed in Phase III clinical testing.
- [NB: Only case studies, no random selection or otherwise representative cases]

- Phase III studies did not confirm Phase II findings of
  - efficacy in 14 cases,
  - safety in 1 case, and
  - both safety and efficacy in 7 cases.

- These unexpected results could occur even when the Phase II study was relatively large and even when the Phase II trials assessed clinical outcomes or when the product was already approved for another condition (n = 7).

Source: 22 Case Studies Where Phase 2 and Phase 3 Trials Had Divergent Results
https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM535780.pdf

- FDA paper was “not intended to assess why each of these unexpected results occurred or why further product development was not pursued. Rather, these cases, chosen from a large pool of similar examples, illustrate the ways in which controlled trials of appropriate size and duration contribute to the scientific understanding of medical products.”

Source: 22 Case Studies Where Phase 2 and Phase 3 Trials Had Divergent Results
https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM535780.pdf

Vaccines

- Experimental HSV-2 Vaccine (Chiron, now Novartis)
  - Two Phase II studies randomized over a hundred persons with no antibodies to HSV-2 and showed that the vaccine induced an antibody response (similar to natural infection).
  - Two Phase III RCTs followed, involving almost 2,400 persons showed that despite producing an antibody response as before, vaccine recipients acquired HSV-2 infection at a rate similar to placebo (4.6% of placebo group versus 4.2% of vaccine group).
  - Despite positive biomarker results in Phase II, in the Phase III trials the vaccine did not prevent genital herpes.

Source: 22 Case Studies Where Phase 2 and Phase 3 Trials Had Divergent Results
https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM535780.pdf

Monoclonal Antibodies

- Figitumumab (Pfizer)
  - Despite positive clinical results in Phase II for this targeted therapy, adding figitumumab to established chemotherapy regimens in Phase III failed to improve survival, and in combination with one regimen increased serious adverse events and deaths.
  - After the Phase III trials were terminated early for lack of efficacy and safety concerns, Pfizer retracted the article describing the Phase II data. The company discovered that tumor shrinkage had not been confirmed in all responding patients, deviating from Pfizer's standard operating procedures. The corrected data showed a lower response rate.

Source: 22 Case Studies Where Phase 2 and Phase 3 Trials Had Divergent Results
https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM535780.pdf

Tumor Vaccines

- MAGE-A3 vaccine (GlaxoSmithKline)
  - Despite a promising proof of concept trial of this targeted immune therapy against NSCLC, in the Phase III trial the MAGE-A3 vaccine conferred no clinical benefit when compared to a placebo.
  - Phase II: Following surgery to remove as much of the tumor as possible, 182 patients were randomized to receive either the MAGE-A3 vaccine or placebo 13 times over 27 months. The results showed a non-statistically significant improvement in disease-free survival and overall survival among patients receiving this cancer vaccine.
  - Phase III: 2,272 patients were randomized (against placebo) and showed a statistically non-significant increase in disease-free survival (60.5 months vs. 57.9 months).

Source: 22 Case Studies Where Phase 2 and Phase 3 Trials Had Divergent Results
https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM535780.pdf

Coagulation products

- Recombinant Factor VIIa (NovoSeven; Novo Nordisk)
  - FDA approved for treatment of hemophilia.
  - Indication: Reduction of intracerebral bleeding and hematoma size in patients with stroke
  - In a placebo-controlled, double-blinded trial with 399 patients, treatment with rFVIIa within four hours after the onset of a hemorrhagic stroke reduced the amount of bleeding in the brain, reduced mortality, and improved patients' functional outcomes at 90 days.
  - Phase III: 850 patients randomized to three arms showed smaller bleedings, yet no clinical benefit but significant increase in thromboembolic events
  - Despite positive clinical results in Phase II, in the Phase III trials patients with intracerebral bleeding who received recombinant factor VIIa experienced no clinical benefits and an increased incidence of SAEs compared to patients who received placebo.

Source: 22 Case Studies Where Phase 2 and Phase 3 Trials Had Divergent Results
https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM535780.pdf

Translarna

- Indication: Duchenne muscular dystrophy

What benefits of Translarna have been shown in studies?

Translarna was first studied in one main study involving 174 patients with Duchenne muscular dystrophy who were able to walk, where two doses of Translarna (40 mg/kg daily and 80 mg/kg daily) were compared with placebo (a dummy treatment). The main measure of effectiveness was the change in the distance the patient could walk in six minutes after 48 weeks of treatment.

Although an initial analysis of the results of all the data from the study did not show a significant difference in the distances patients in the Translarna and placebo groups could walk, further analyses indicated that walking ability worsened to a lesser extent with 40 mg/kg daily Translarna than with placebo: after 48 weeks of treatment patients receiving 40 mg/kg daily Translarna could walk on average 31.7 metres more than those given placebo. A more pronounced effect was observed in a subgroup of patients whose ability to walk was worsening, where patients taking 40 mg/kg daily Translarna could walk on average 49.9 more than those taking placebo. The beneficial effect of the lower dose was also supported by improvements in other measures of effectiveness, including those directly linked to patients' daily activities. No improvement was seen with the higher dose (80 mg/kg/day).

A further study in 230 patients with worsening walking ability was completed after initial approval, but its results were considered inconclusive. However, data indicated that Translarna had a positive effect on different measures such as time to run/walk 10 metres, time to climb and descend 4 steps and time to loss of walking ability. In both studies, the beneficial effects of Translarna seemed to be more evident in those patients with moderate decline of their disease.

Conditional approval

At the CHMP meeting in November 2016 within the annual renewal procedure for Translarna, having assessed the submitted results of the outstanding specific obligation, the CHMP concluded that although the imposed study had been conducted it had not led to comprehensive clinical data confirming the positive benefit–risk balance in the concerned indication and therefore recommended imposition of a new specific obligation in order to generate further clinical data.

Discussion

- Early involvement of all stakeholders (patients, applicant, regulators, HTAs, payers) might help for better drug development and faster licensing.
- Uncertainties remain when granting Conditional Approval.

  - The possibility and methods to revert / alter decisions (on all levels) are of particular importance.

- RWE/RWD might help to mitigate risks and to make well informed decisions, but requires more work from all sides (definition, methods, interpretation of results).
- Of note, RWE is no magic bullet.
- Proper RCT should remain the (gold) standard whenever possible.