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Recent qBRA History

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Recent history in qBRA

2011
- BRAT

2012
- ICH PBRER Guidelines
- FDA/CDRH Benefit-Risk Worksheet

2014
- **EMA Benefit-Risk Methodology Project**

2015
- **IMI-PROTECT**
- FDA/CDER-CBER BRF implemented

2016
- ICH Clinical Overview Guidelines
- **ISPOR MCDA good practices report**

2020
- **EMA Regulatory Science to 2025 Strategy**

2021
- **FDA/CDER-CBER Draft Guidance on Benefit-Risk Assessment**

Happening in parallel: Advances in patient input

Foundation: Academic and methodological research

Current regulatory emphasis is on structured, descriptive approaches…

- EMA and FDA utilize a **textual/narrative description** of the therapeutic context, benefits, risks, and conclusions to support the benefit-risk assessment for their decision-making
- ICH guidelines suggests a similar approach for sponsors for marketing applications and post-market reporting
- Some unique features:
  - EMA: PrOACT-URL and **effects table**
  - FDA Drugs & Biologics: **Benefit-Risk Framework**
  - FDA Devices: question-based **worksheet**

Day 80 assessment report – Overview and D120 LOQ template with guidance (Rev 08.21): https://www.ema.europa.eu/ documents/template-form/day-80-assessment-report-overview-d120-loq-template-guidance-rev0821_.docx
ICH M4E: https://database.ich.org/sites/default/files/M4E_R2__Guideline.pdf
ICH E2C: https://database.ich.org/sites/default/files/E2C_R2_Guideline.pdf
Benefit-Risk Assessment for New Drug and Biologic Products (Draft, Sep 2021): https://www.fda.gov/media/152544/download
Benefit-Risk Determinations for Medical Devices (Aug 2019): https://www.fda.gov/media/99769/download

…but quantitative approaches are allowed…

- EMA recognizes “quantitative” approaches as an option for evaluating the benefit-risk balance and tradeoffs
  - EMA Benefit-Risk Methodology Project **endorsed use of MCDA**
  - IMI-PROTECT recommendations recognized **role for qBRA when the preferred choice is not obvious**
- ICH guidelines mention methods to “quantitatively express the underlying judgments and uncertainties” and to “**compare and/or weigh benefits and risks**” can be used
- FDA draft guidance for Drugs & Biologics indicates **additional analysis may add value** for challenging benefit-risk assessments
  - Estimating clinical outcomes
  - Modeling real-world benefits and risks
  - Integrating benefits and risks in a combined analysis

EMA BR Methodology Project Work Package 4: https://www.ema.europa.eu/en/documents/report/benefit-risk-methodology-project-work-package-4-report-benefit-risk-tools-processes_en.pdf
Hughes et al. PDS. 2016;25(3):251-262 https://onlinelibrary-wiley-com.fda.idm.oclc.org/doi/full/10.1002/pds.3958

…and growing

- EMA Strategy 2025 includes plans to enhance structured benefit-risk assessment and promote use
- FDA
  - Drugs & Biologics:
    - Several uses of techniques to model real-world public health outcomes, including for the **Pfizer COVID-19 vaccine for ages 5-11**
    - First application by the Agency of **qBRA to inform a drug approval**
  - Devices
    - Several applications of patient preference information and resulting benefit-risk assessments, including: weight loss devices, in-home hemodialysis, and **ear tube delivery systems**

EMA Regulatory Science to 2025: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/ema-regulatory-science-2025-strategic-reflection_en.pdf

Increasing interest in patient input parallels and supports qBRA

- Increasing culture change to emphasize the **role of patient voice** in medical product development and regulatory decision-making to understand the unmet need and interpret what is important and meaningful to patients
  - EMA: Framework for Engagement
  - FDA/Drugs: Patient Focused Drug Development public meetings, voice of the patient reports, and guidance series
  - FDA/Biologics: Patient Engagement Program
  - FDA/Devices: Science of Patient Engagement Program
- Recent methodological advances for patient preferences specifically:
  - **IMI-PREFER** recommendations, finalized in 2022, cover the “why, when, and how” of preferences for medical products

Framework for Engagement: https://www.ema.europa.eu/en/documents/other/engagement-framework-european-medicines-agency-patients-consumers-their-organisations_en.pdf
Patient Focused Drug Development: https://www.fda.gov/drugs/development-approval-process-drugs/cder-patient-focused-drug-development
Patient Engagement Program: https://www.fda.gov/vaccines-blood-biologics/development-approval-process-cber/center-biologics-evaluation-and-research-patient-engagement-program
Science of Patient Engagement Program: https://www.fda.gov/about-fda/center-devices-and-radiological-health/cdrh-patient-science-and-engagement-program
IMI-PREFER Recommendations: IMI-PREFER recommendations: https://www.imi-prefer.eu/recommendations/

Regulatory guidance for PPI is also emerging

- Regulatory guidance **exists from FDA in Devices**
  - PPI is an explicit consideration in Agency benefit-risk assessments
  - Guidance is available and a list of preference-sensitive areas maintained
- Guidance **from others is proposed**
  - ICH: patient preference included as a proposed topic for future ICH guidelines
  - FDA Drugs & Biologics
    - PPI mentioned in the draft benefit-risk guidance
    - Guidance is included in the PDUFA VII (FY2023-27) Commitment Letter
  - EMA Strategy 2025: PPI guidance identified as a priority

Patient Preference Information (Aug 2016): https://www.fda.gov/media/92593/download
Preference-sensitive priority areas for medical devices: https://www.fda.gov/about-fda/cdrh-patient-science-and-engagement-program/list-patient-preference-sensitive-priority-areas
Reflection Paper: https://admin.ich.org/sites/default/files/2021-06/ICH_ReflectionPaper_PFDD_FinalRevisedPostConsultation_2021_0602.pdf
PDUFA VII Draft Commitment Letter: https://www.fda.gov/media/151712/download

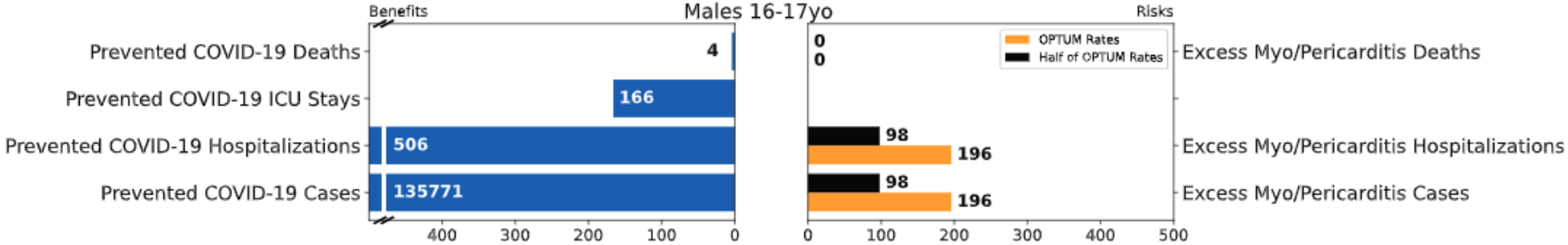
Examples from FDA

Semi-quantitative benefit-risk assessment: COVID-19 Vaccine & risk of myo/pericarditis

- Estimated benefits and risks per 1 million individuals with a completed vaccine series (2 doses), modeled over a 6-month period
- Three Scenarios:

Scenario	VE-case	VE-hosp.	COVID-19 case inc.	COVID-19 hosp. inc.	Vaccine attributable myo/pericarditis death rate
Base	90%	90%	July 10, 2021	July 10, 2021	0%
Most Likely	70%	80%	10 x July 10, 2021	4 x July 10, 2021	0%
Worst-Case	70%	80%	July 10, 2021	July 10, 2021	0.002%

- Results for males 16-17 yo (group at highest risk of myo/pericarditis), for the most likely scenario:



Funk, et al. Vaccine. 2022; 40(19):2781-2789: https://www.sciencedirect.com/science/article/pii/S0264410X22003292
Summary basis for regulatory action: https://www.fda.gov/media/151733/download

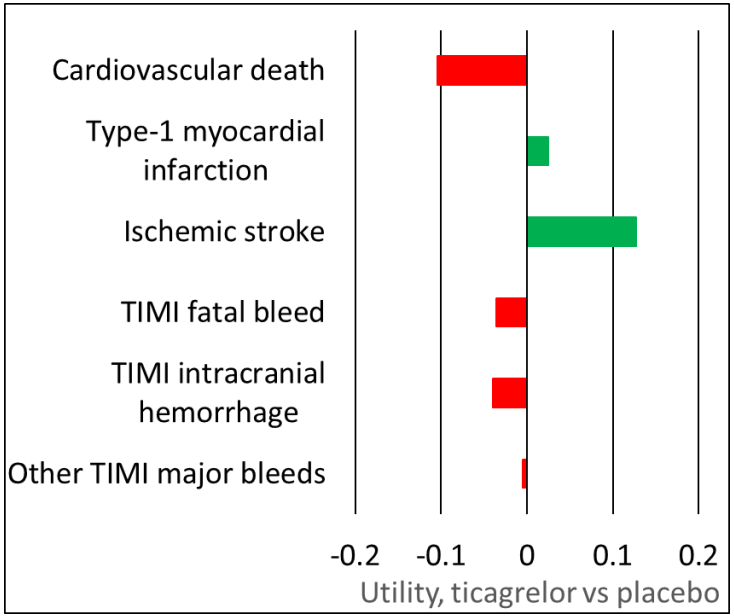
PPI to set a performance goal: Tula System for ear tube placement

- The Tula System is intended for the placement of ear tubes as an in-office (ambulatory) procedure with local anesthesia
  - **Benefits:** successful attempt with the Tula System avoids the need for an operative procedure with general anesthesia
  - **Risks:** failure of an attempt with the Tula System would necessitate an operative procedure under general anesthesia in addition to the attempt with the Tula System
- Patient (parent) preferences used to establish the performance goal for success rate: **parents would prefer an attempt with the Tula System if the success rate were at least 68%**
- Success rates from the pivotal trial were 87%

Summary of Safety and Effectiveness (pages 22, 38): https://www.accessdata.fda.gov/cdrh_docs/pdf19/P190016B.pdf

qBRA using MCDA and regulator preference: Ticagrelor for cardiovascular prevention

- Trial showed ticagrelor **prevented fewer cardiovascular events than bleeds caused**; also found a small imbalance in cardiovascular death
- Applied **MCDA with reviewer preferences** given by two members of the FDA review team
- **Conclusion:** given variability in the tradeoffs between the two reviewers and uncertainty in the direction of effect of cardiovascular death risk estimates, it is reasonable to conclude that there may be patients who would accept the benefit-risk balance
- **Result:** approval for prevention of MI and stroke, with labeling to convey the benefit-risk balance



Results for one of the two reviewers

Lackey, Garnett & Senatore. Circulation. 2021;144:655-658: https://www.ahajournals.org/doi/full/10.1161/CIRCULATIONAHA.120.053294
Review documentation: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/022433Orig1s028.pdf

Final thoughts

- Confluence of interest in qBRA and associated methodologies in recent years
- Availability of peer reviewed, consensus good practice recommendations supports further utilization
- FDA employs a range of approaches to inform benefit-risk assessment and the regulatory decision, including qBRA, depending on the context