Fast to market *versus* robustness of data

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Disclaimer

This work represents the views of the presenters and not those of J&J.

Agenda

Lots of questions

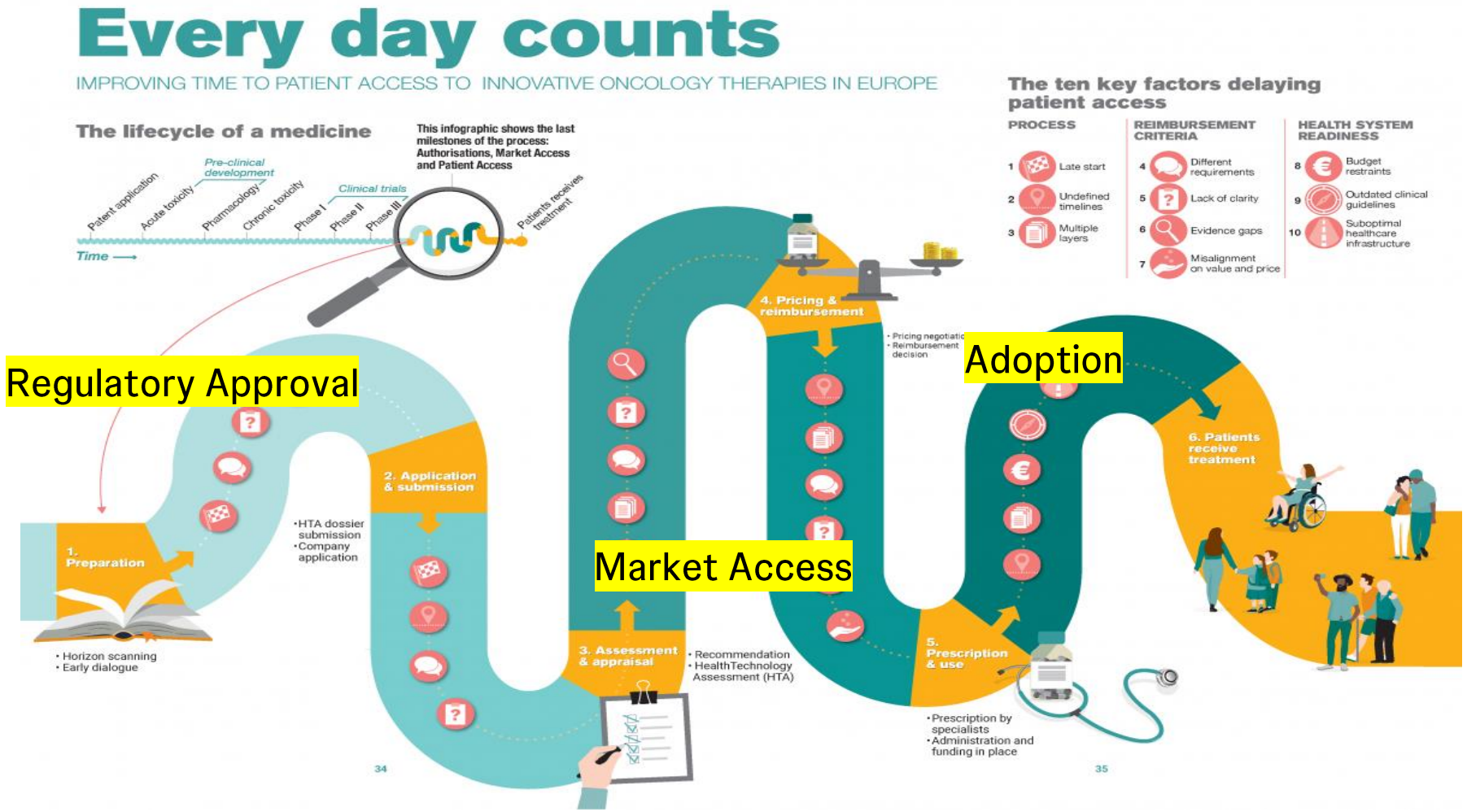
- Time matters - What is FAST?
- Going Fast & Furious (F&F) today?
- What are the trade-offs?
- What is good enough for HTA?
- How successful are we when we do FAST?
- Take-home messages

This is a Workshop and, as such, we would like to

- **Raise questions**
- **Raise awareness**
- **Raise alignment**

Time Matters

Evidence package produced for regulatory filing has an impact on probability of access and time to access.



White-paper-every-day-counts-improving-time-to-patient-access-to-innovative-oncology-therapies-in-europe_from-EFPIA_and_Vintura.pdf

FAST – to which destination?

Triple A – Approval, Access, Adoption

Time to patients being able to use medication takes into account 3 key steps – approval, access and adoption

Time to Regulatory Approval

Time from Regulatory Approval to Market Access

Time from Market Access to Adoption- Patient Access to medication/technology.

Fast & Furious usually translates in ….

Clinical Study designs which are faster as they may require fewer resources and budget

- **Single Arm** Trials
- **Placebo/Standard of Care** controlled trials – *versus* active comparator arms
- **Non-randomized** comparative multi-arm trials
- Single Arm trials with use of **external comparators**
- Trials in a **sub-populations** with (potentially) *generalizability issues*
- (More recently in Oncology) Phase I Expansion cohorts (**non-comparative** and **non-randomized**)

These designs may be the only ones *feasible*, however, they can (and do) lead to regulatory conditional approvals.

Trade-offs to consider when "*going F&F*"

What is the ultimate objective?

- RCT *versus* uncontrolled trial
  - Feasibility of alternative trial designs
  - Certainty *versus* uncertainty
  - Resources and budget required to implement
  - Extent of experience (robustness *versus* limited)
  - Regulatory and HTA acceptability

Trade-offs reflect the different objectives/KPI's of the stakeholders (stakeholders for approval, access, adoption require specific evidence/processes).

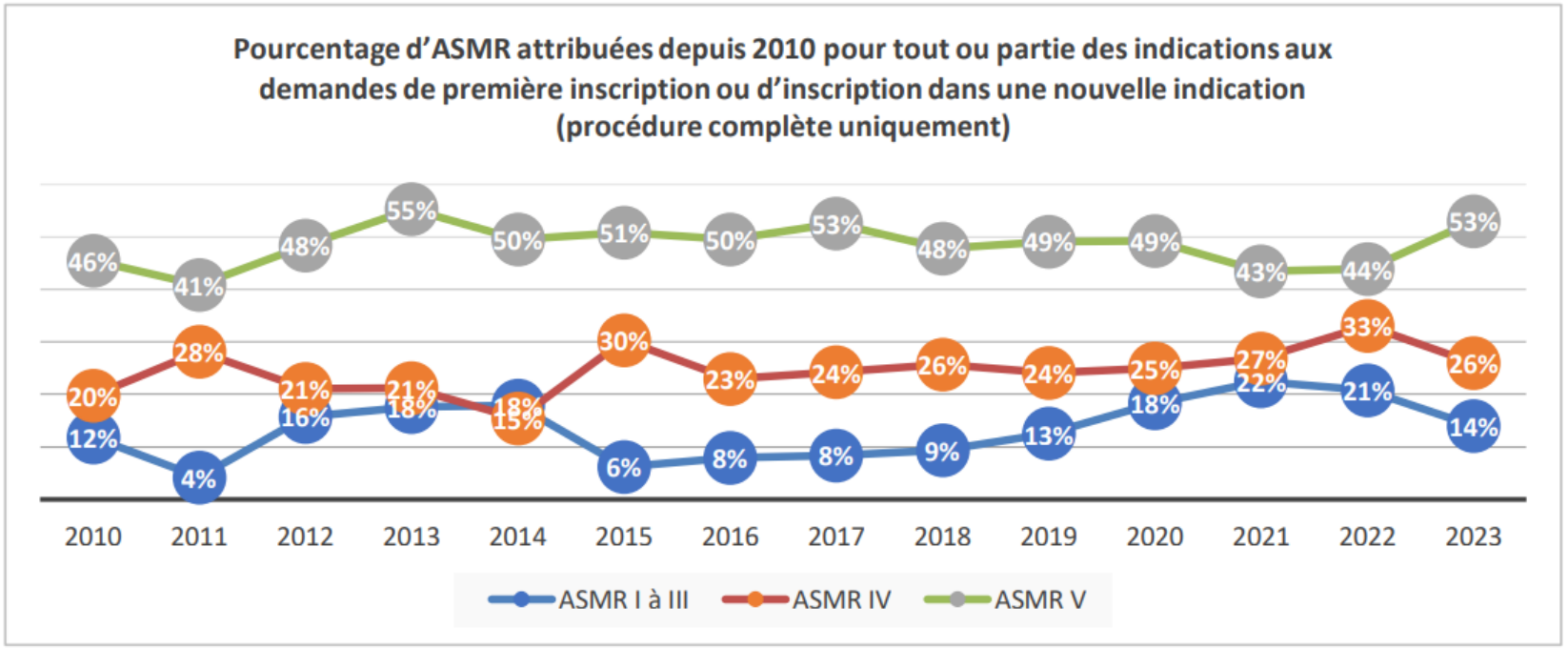
Can some short-term gains (faster regulatory approval) lead to long-term disadvantages, i.e. negative trade-off?

RCT = Randomized Controlled Trial

HTA outcomes(2010-2023)

HAS example - ASMR ratings over time for new indications/new tx

ASMR attribuées depuis 2010 pour tout ou partie des indications aux demandes de première inscription ou d'inscription dans une nouvelle indication (procédures complètes uniquement)



Amélioration du service médical rendu
ASMR I: major improvement;
ASMR II: important improvement;
ASMR III: moderate improvement;
ASMR IV: minor improvement;
ASMR V: no improvement

What are the HTA outcomes when we go FAST in clinical trial design approaches?

https://www.has-sante.fr/upload/docs/application/pdf/2024-06/rapport_dactivite_2023_de_la_ct.pdf

What is needed for HTA?

HTA desired evidence is RCT evidence

- Single arm trials are seen to increase the uncertainty of the results, and increase risk of bias
- Justification for single arm studies is key - considered exceptional, highly contextualized
- Methodological considerations – robust systematic collection of data sources, target trial emulation, external control selection, *etc*

HTA bodies recognize the importance of reducing time to access for patients – some have shown interest in finding ways of adapting trial designs for faster execution while providing sufficient evidence to reduce uncertainty of results

- e.g. adaptive designs, platform trials, seamless trials, pragmatic trials etc.
- Methodological challenges still remain

HTA Agencies have their own remit, guiding principles and methods that need to be taken into account.

Single arm studies, external control use & HTA outcomes

Table 3. NICE single-arm trial oncology submissions by external control data source and external control manufacturer's justification, patient and disease characteristics and final decision-making.

External comparator source	Total NICE SAT submissions N=29	SAT submissions with a biomarker-defined patient population	SAT submissions in an orphan disease indication	Final HTA recommendations			Any EC justification described in the SAT submission
				Positive (routine use)	Use only in CDF	Negative	
Published, aggregate data derived from an RCT or a SAT only	4 (13.8%)	3 (10.3%)	2 (6.9%)	2 (6.9%)	2 (6.9%)	–	4
IPD data derived from an RCT or a SAT only	2 (6.9%)	1 (3.4%)	–	1 (3.4%)	–	1 (3.4%)	1 (3.4%)
Published, aggregate data derived from observational studies only	3 (10.3%)	1 (3.4%)	2† (6.9%)	2 (6.9%)	–	1‡ (3.4%)	3 (10.3%)
IPD data derived from RWD only	–	–	–	–	–	–	–
Concurrent internal controls only	1 (3.4%)	–	–	–	–	1 (3.4%)	1 (3.4%)
Multiple sources (combination of the above)	19 (65.5%)	9 (31.0%)	7† (17.2%)	9 (31.0%)	10 (34.5%)	–	19 (65.5%)

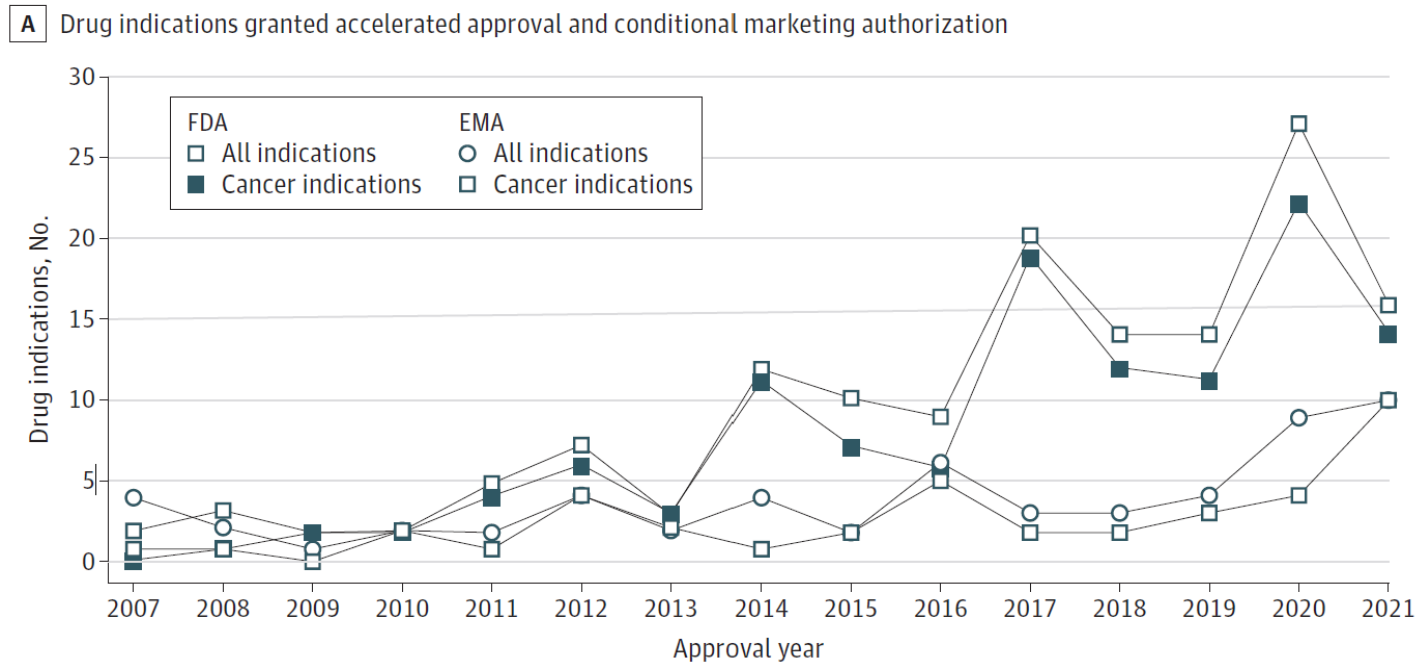
†Three submissions had orphan drug status at the time of submission which has since been withdrawn.
‡One submission assessed two populations, one of which received a negative recommendation and one which was recommended in the CDF.
CDF: Cancer Drugs Fund; EC: External control; HTA: Health technology assessment; IPD: Individual patient data; NICE: National Institute for Health and Care Excellence; RCT: Randomized controlled trial; RWD: Real-world data; SAT: Single-arm trial.

Justifying the source of external comparators in single-arm oncology health technology submissions, Appiah et al 2024

Conditional approval EU 2007 - 2021

Does speed pay off?

- From 2007 to 2021, 58 indications (all first approvals) were granted conditional approval; 40 of these (69%) were oncology indications;
- Therapeutic rating was available for 56/58 (97%) of the indications from HAS, CADTH, G-BA;
- At the time of HTA approval, 21/56 (**38%**) were found to have additional therapeutic benefit (31%, 12/39) for cancer *versus* (53%, 9/17) for noncancer indications in the EU);
- Uncertain nature of the data supporting the drugs approved through these pathways may have played a role in the benefit ratings observed.



Bias may be incurred as

- withdrawn applications not accounted for
- If one country reimborses then it's a "Yes"

Therapeutic Value of Drugs Granted Accelerated Approval or Conditional Marketing Authorization in the US and Europe From 2007 to 2021, Volkinger et *al.* JAMA, 2022

Perception of conditional approval in England, Scotland , France and Canada

How do HTA agencies perceive conditional approval of medicines? Evidence from England, Scotland, France and Canada, Mills and Kanavos 2022

- There is a clear and growing *disconnect* between regulatory and reimbursement agencies, that require **robust and different evidence** to decide on funding.
- Approx. 30-40% of compounds approved conditionally require either HTA resubmission or are rejected.
- A wide range of uncertainties, both economical and clinical unresolved issues, are raised by HTA agencies.
- HTA outcomes remain highly variable: in particular, *disease severity* and *unmet medical need* are **not sufficient to dissolve such uncertainties**.
- NICE was the most favorable, with positive recommendations to 93% (14/15) indication appraised.
  HAS also had a high reimbursement rate (only one product received an SMR rating of “insufficient”),
  no products received an ASMR of I or II (indicating a “major” or “important” added benefit, respectively) and
  33% received a V rating (non-existent added benefit or “lack of therapeutic progress”.

Perception of conditional approval in England, Scotland, France and Canada

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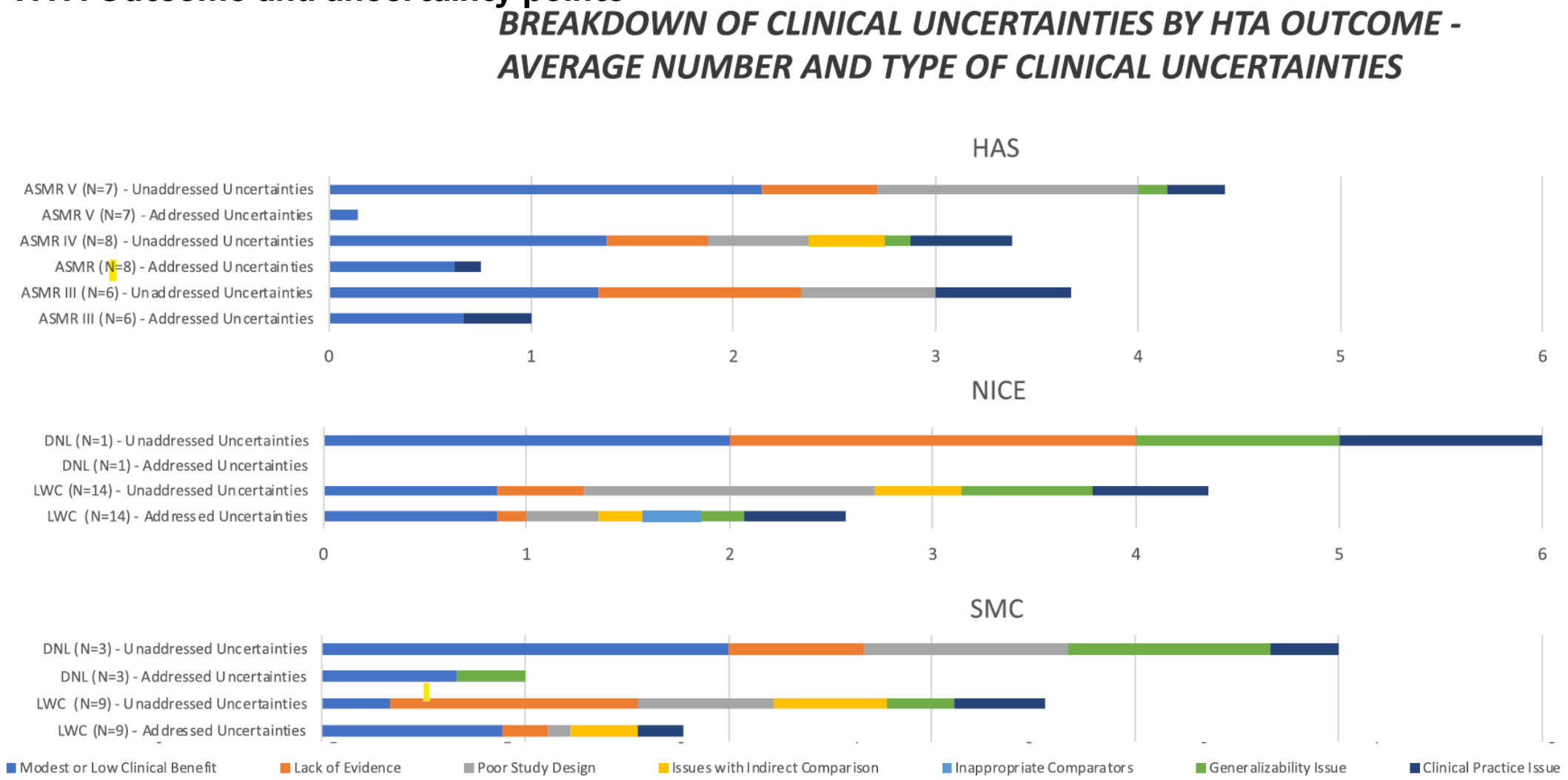
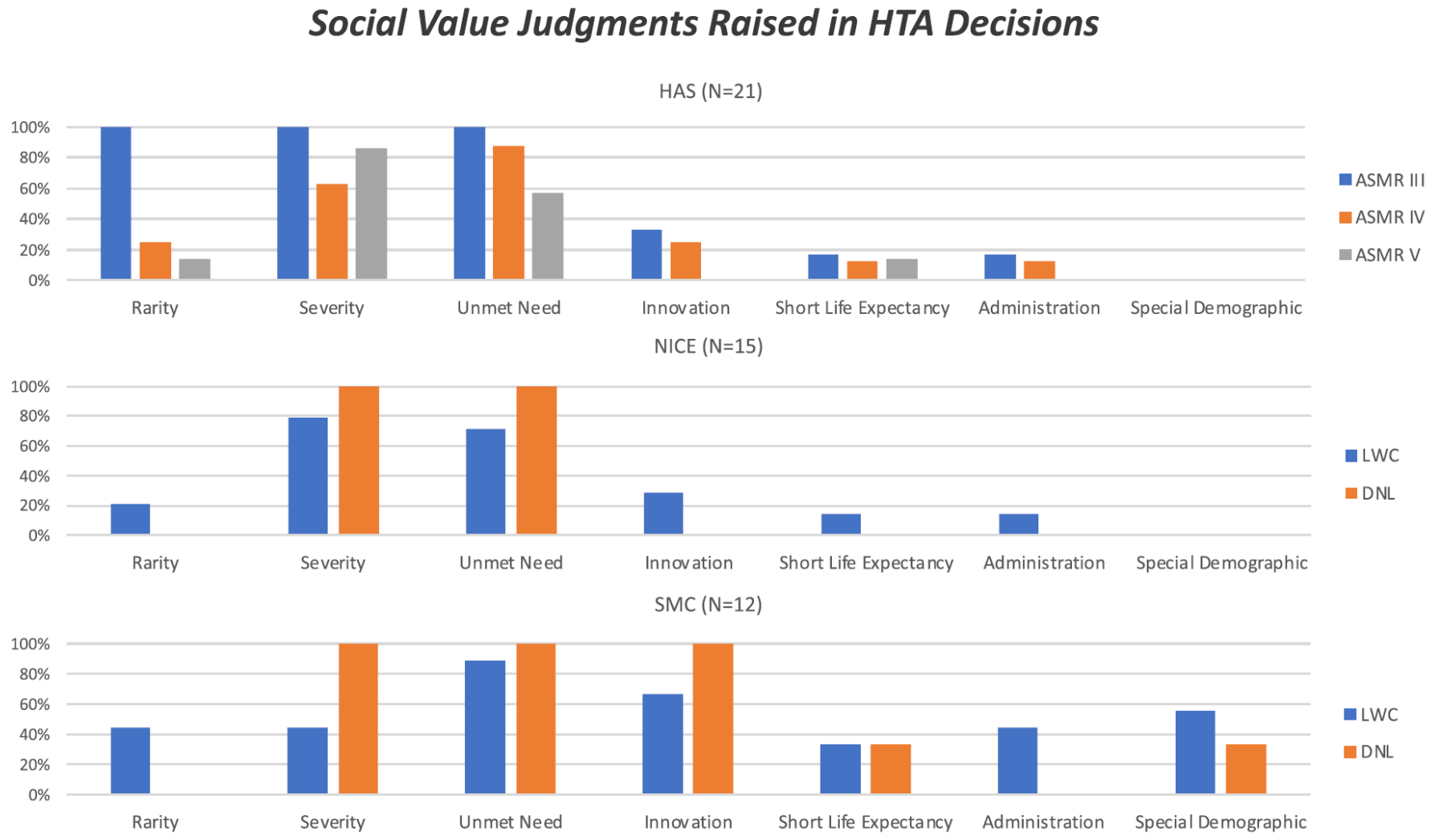
HTA Outcome and uncertainty points



Perception of conditional approval in England, Scotland, France and Canada

Low value rating even when unmet need

How do HTA agencies perceive conditional approval of medicines? Evidence from England, Scotland, France and Canada,
Mills and Kanavos 2022



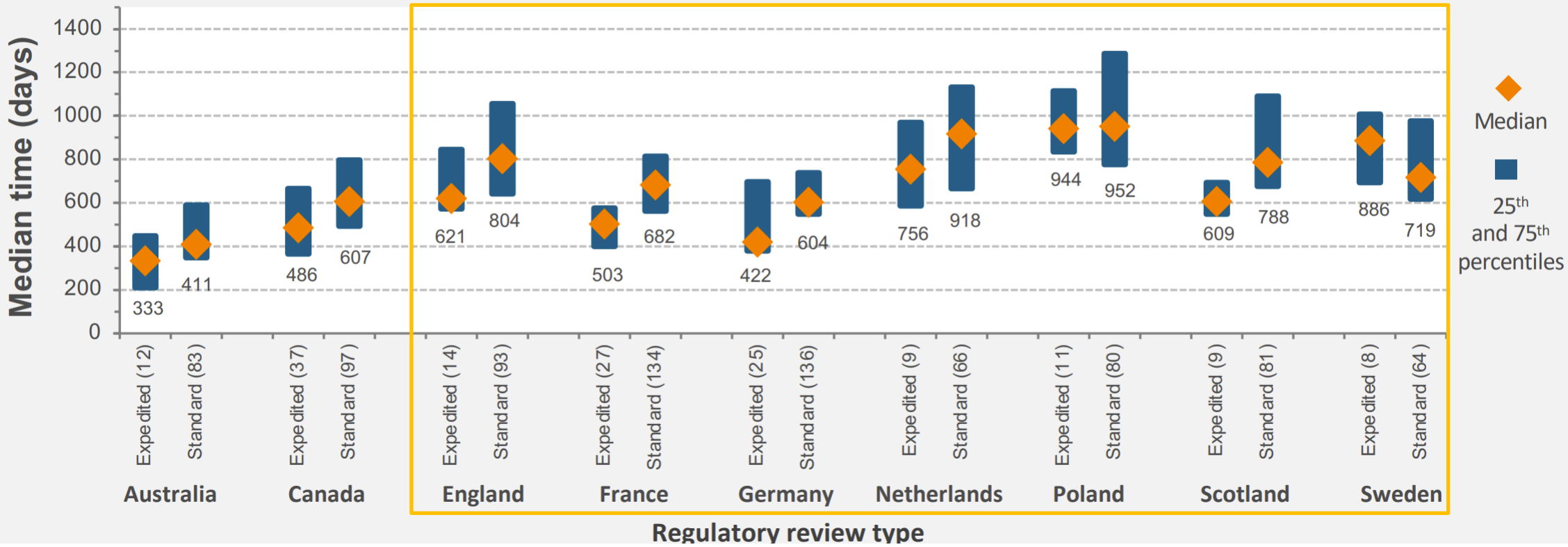
Synchronization of Regulatory and HTA outcomes 19-23

Time is of essence

- In all countries assessed, except Sweden, the median overall time from regulatory submission to HTA recommendation was shorter for products undergoing ***expedited review*** (as compared to standard process).

Time taken from regulatory approval to HTA recommendation includes
- Company submission strategy
- Company time for pre-submission preparation
- HTA agency review time

Figure 15. Time taken from regulatory submission to HTA recommendation (2019-2023) by regulatory review type



CIRS HTADock Project: Review of HTA outcomes and timelines in Australia, Canada, Europe and the UK 2019-2023

You think you're driving a sports car....

... but look closer

Phase I evidence in oncology

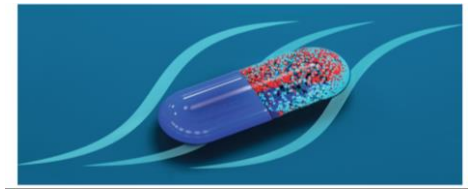
New entry in the SAT's evidence world: dose expansions

GUIDANCE DOCUMENT

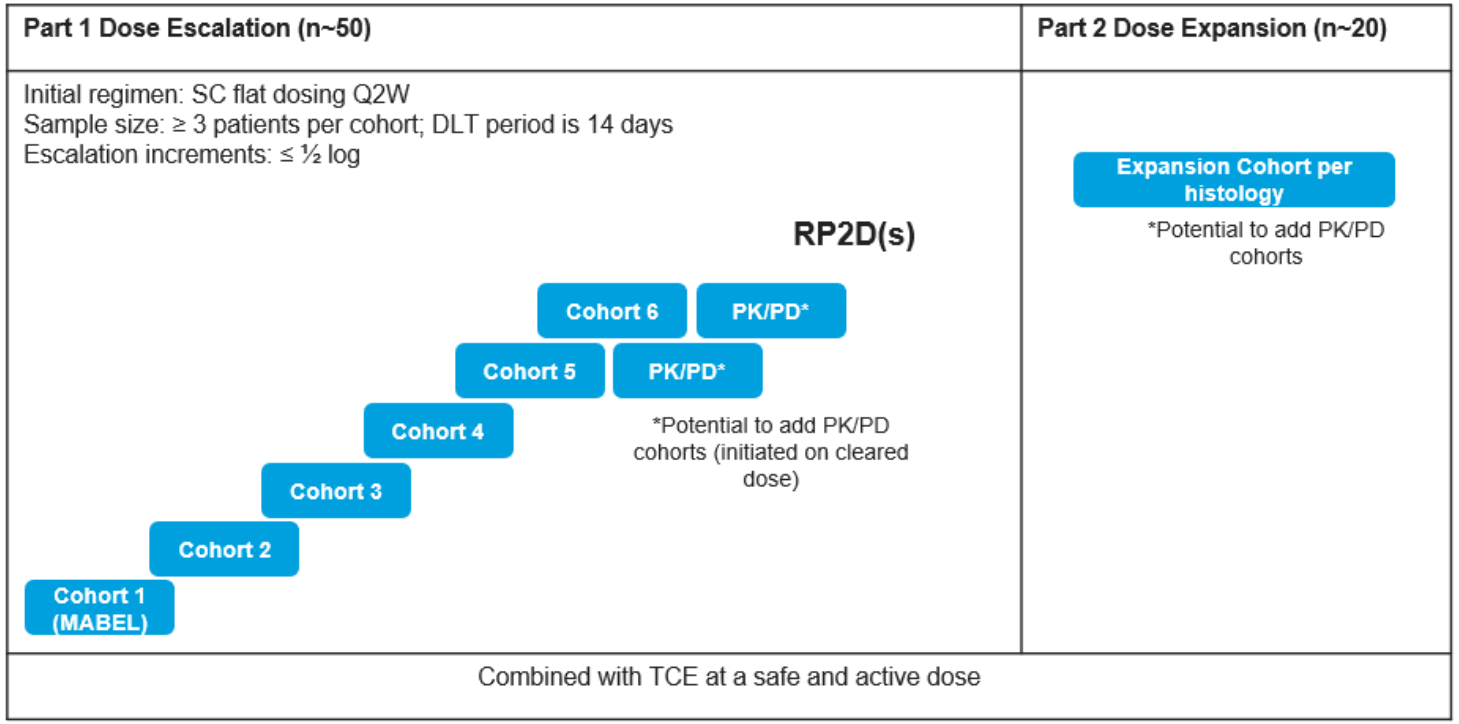
Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases

Draft Guidance for Industry; Availability

JANUARY 2023

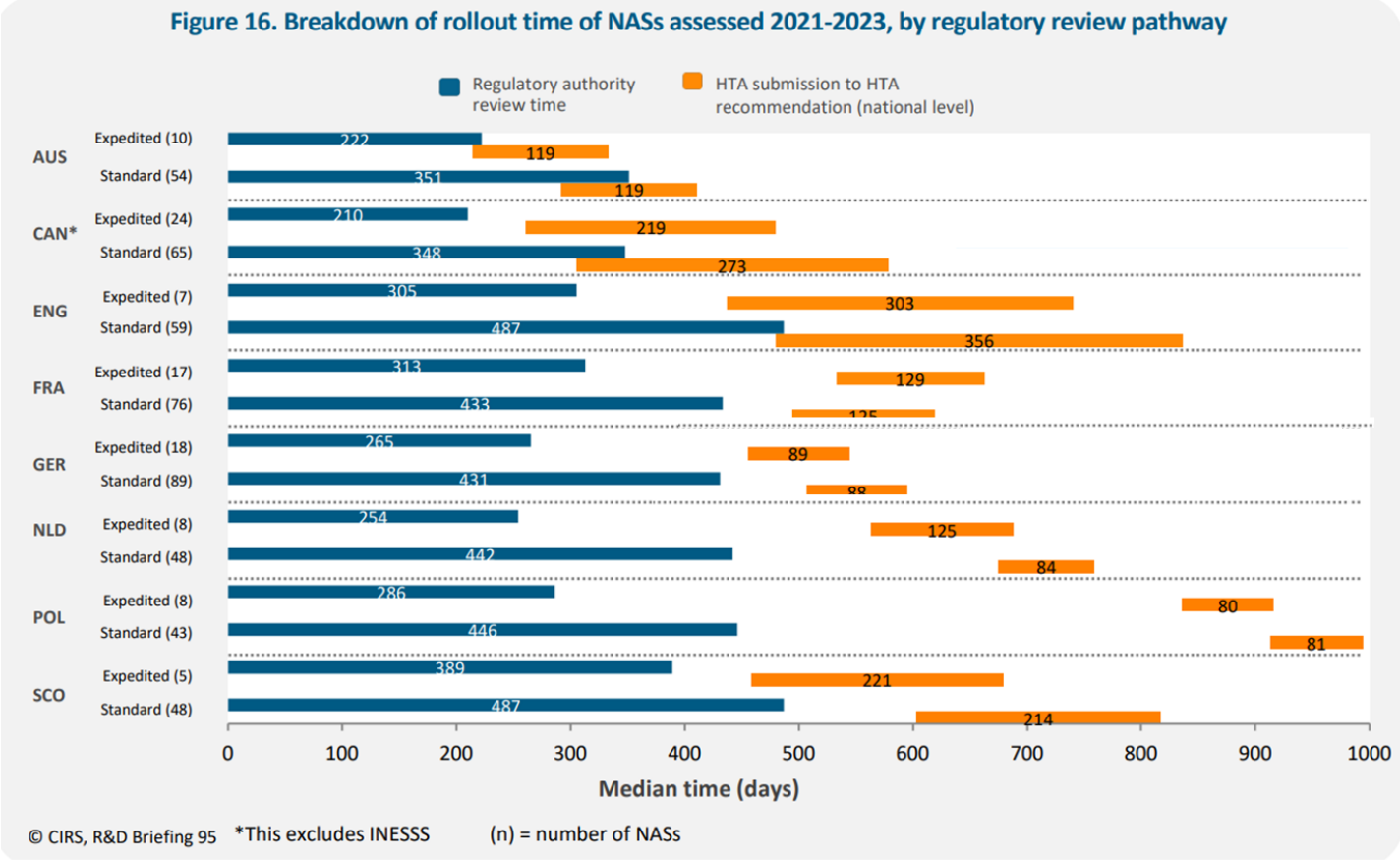


- Typical dose-escalation (up to 100 patients) and then expansion paradigm (20 or so patients);
- Project Optimus guidelines from 2023 (FDA) initiative to optimize dosing;
- Phase I's are the basis of the dose identification and are *more and more often* integral part of the submission package;
- Uncertainty on the dosing may weigh in on Phase IV when compound already approved.



‘FAST’ patient access – HTA pathways

- HTA submission *time* generally similar irrespective of regulatory pathway
- To expedite patient access in specific circumstances
- Examples of HTA pathways/approaches to increase capacity for review and support health resource allocation decision-making
  - HAS “accès précoce”
  - Germany – e.g. orphan drugs, 50 million EUR threshold SHI Expenditure
  - NICE “proportionate approach”, Rapid Entry to Managed Access
  - Time-limited recommendations with evidence collection



https://www.nice.org.uk/about/what-we-do/proportionate-approach-to-technology-appraisals

Sola-Barrado B, Cervelo-Bouzo P, Wang T, McAuslane N. 2024. R&D Briefing 95: Review of HTA outcomes and timelines in Australia, Canada and Europe 2019 -2023. Centre for Innovation in Regulatory Science. London, UK

https://www.ncbi.nlm.nih.gov/books/NBK594388/

Strategic points to consider

- Does launching *fast/early/conditionally* outweigh potential impacts on clinician experience?
- How does the evidence (if not *final/complete*) impact the price negotiations or even *only* the rating? When is it “good enough” to launch **and** have an acceptable rating/price?
- How do we weigh that the optimal launch sequence may need to vary by country?
- Would any evidence need to come in Phase IV, if earlier is not planned for? Would this be too late then (e.g. for HTA agencies)?
- Can outcomes based or other pricing schemes address uncertainty in data and/or indication based value differentials?

Take-home messages

Could we be FAST but less FURIOUS?

- Better tailor the HTA resources to the conditional approvals, playing a more active role in the evidence generation for conditional approval.
- Sponsors to think much more in advance about the HTA hurdles when it comes to conditional approval and connecting with the reimbursement counterparts.
- As HTA at times requires resubmissions or leads to reduced/delayed access, is this time “loss” factored in formally?
- JCA (Joint Clinical Assessments) will provide a unique opportunity to get regulatory packages ready for the 4th Hurdle.

References

- EFPIA WAIT (**W**aiting to **A**ccess **I**nnovative **T**herapies) indicator – June 24 – https://efpia.eu/media/vtapbere/efpia-patient-wait-indicator-2024.pdf
- How are single-arm trials perceived in heath technology assessments for chronic leukaemia across the EU5, Australia and Canada? Barwood et *al*. ISPOR 2019
- Use of External Comparators for Health Technology Assessment Submissions Based on Single-Arm Trials, Patel et *al*., Value In Health 2021
- Justifying the source of external comparators in single-arm oncology health technology submissions: a review of NICE and PBAC assessments, Appiah et *al*., J Comparative Effectiveness Res, 2024
- Therapeutic Value of Drugs Granted Accelerated Approval or Conditional Marketing Authorization in the US and Europe From 2007 to 2021, Volkinger et *al*., JAMA Health Forum, 2022
- How do HTA agencies perceive conditional approval of medicines? Evidence from England, Scotland, France and Canada, Mills and Kanavos, Health Policy, 2022
- Early market access of cancer drugs in the EU, Martinalbo et *al*., Annals of Oncology 2015