Improving Access to Anti-tuberculosis Drugs for Children: Updates from the World Health Organization

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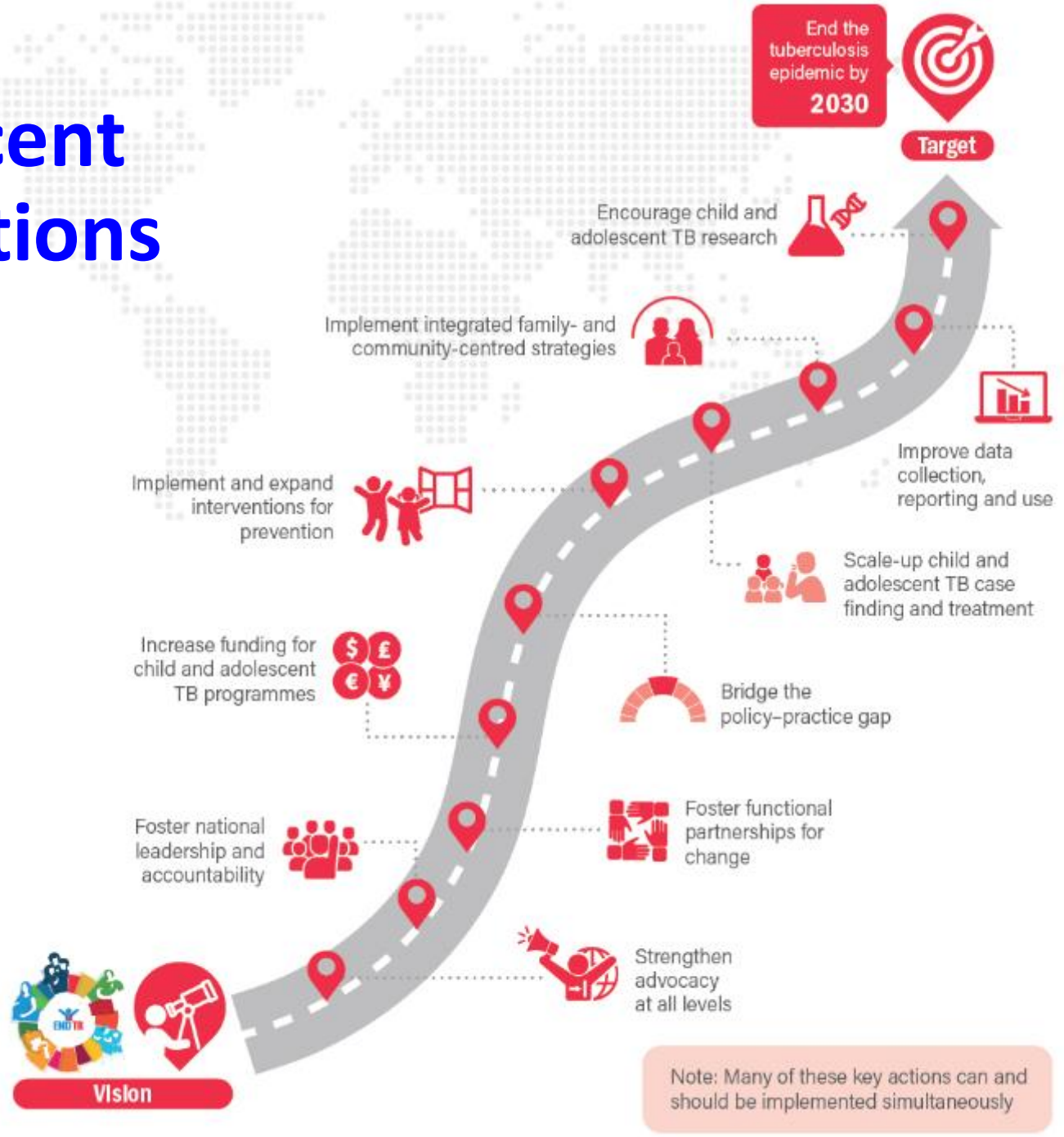
Child and Adolescent Roadmap: Key actions

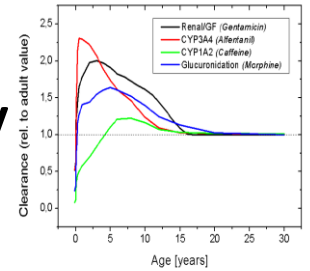
Roadmap towards ending TB in children and adolescents

Leveraging HLM commitments and synergise with other partners particularly around promoting innovation and integrating services to improve children outcomes



Developing medicines for children requires addressing unavoidable complexities

- Disease natural history
- Growth and puberty: dosing the same drug in changing body and a changing brain
- Drug metabolism is different from adults and can heavily depend on genetic polymorphisms (i.e. EFV)



- Key comorbidities that impact drug use, tolerability, and toxicity in SSA (HIV, TB, malaria, malnutrition, anemia, etc.)
- Palatability and ease of administration are critical to support adherence

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…while promoting **simplification and harmonization** across the age spectrum

Care taker

- Same regimen for all family members may be helpful
- Avoid inappropriate drug sharing

Health care Provider

- More familiar with adult regimens
- But different formulations still need to be available
- Dosing changes still necessary as child grows/ages

Programme /supply manager

- Streamline procurement
- Simplify forecasting and ordering

Manufacturers

- Ensure API availability
- Lower cost of production

Harmonization is critical but when formulations are different benefits of harmonization are potentially limited

Development of **scored dispersible adults tablets** becomes essential

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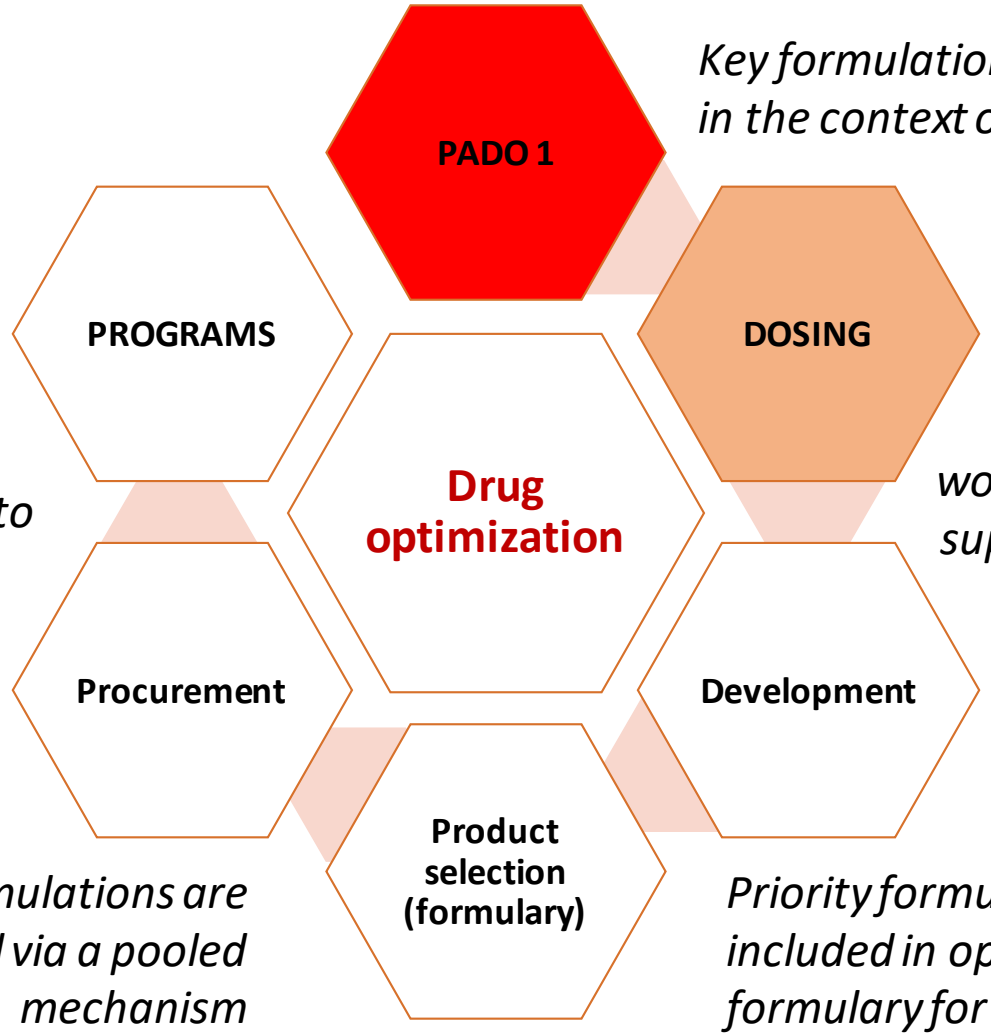
Drug optimization for paediatric TB through collaborative and coordinated action



Key formulations are prioritised in the context of a public health approach

Priority formulations are reliably supplied to countries

Technical/research work is undertaken to support development of the priority formulations

Priority formulations are procured via a pooled mechanism

Priority formulations are included in optimal formulary for selection

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Key lessons learned

- Critical to connect drug and formulations development with guidelines revision and adoption
- Optimizing trial design to shorten timelines for investigation (ie PIPs/PSPs) is possible
- Early investigation of acceptability can support definition of TPP and better inform formulation development
- Use of existing pathways for acceleration of national registration should be promoted
- Advance planning for introduction is critical to enable timely roll out
- Support to product selection and use of great value to reduce market fragmentation and optimal clinical outcomes
- Pharmacovigilance of great importance to ensure safe introduction of products with limited clinical experience

The 1st PADO TB meeting: Objectives

1. Discuss the PADO for TB platform and modus operandi
2. Develop a list of short/medium and long-term priorities for paediatric TB drug optimization
3. Agree on a way forward to accelerate development and uptake of priority formulations

February 14-15th 2019, Geneva-Switzerland

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A diverse set of expertise to ensure 360 view on the challenges and opportunities

- NTPs from TB high burden and priority countries
- Clinicians
- Scientists
- Funders
- International organizations/technical partners

1: Introduction to size and specifics of paediatric anti-TB drug market
2: Experiences with anti-TB drug development and market shaping
3: Current adult and paediatric TB research landscape
4: PADO for TB
5: Group work to define priorities
6: Where do we go from here?

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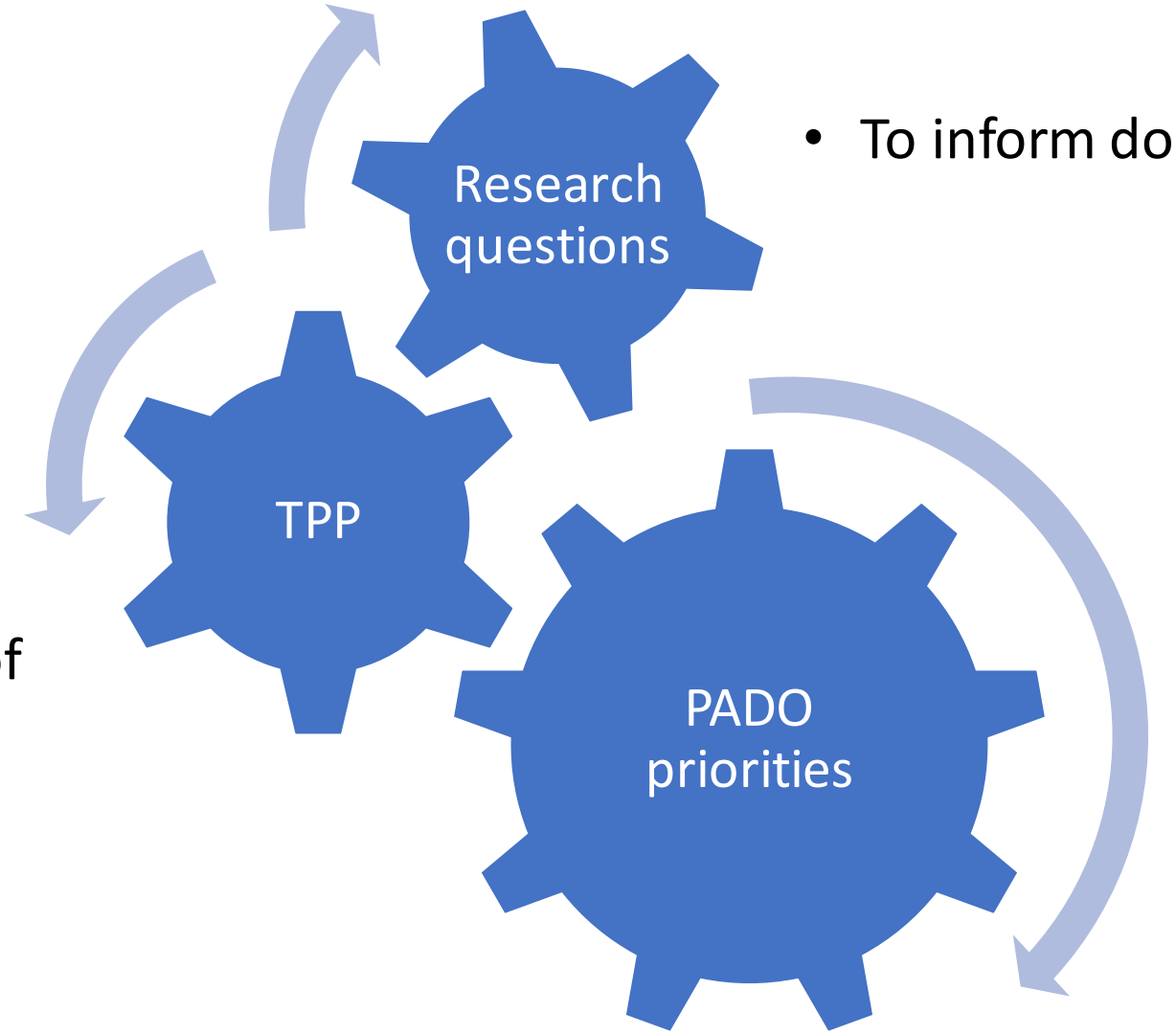
The 1st PADO TB was tasked to initiate the drug optimization process



- To inform dosing OR use

- Consider the full set of possible formulations
- Innovative delivery

- Short and Mid-term priorities 3-5 years
- Long-term priorities (WATCH LIST) 5-10 years

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Short-term list	DS-TB	DR-TB	LTBI	Remarks
Rifampicin (RIF)	√			NOT for 4R LTBI regimen
Rifapentine (RPT)	√		√	
Bedaquiline (BDQ)		√	(√)	On watch-list DR-TB LTBI
Clofazimine (CFZ)		√		
Delamanid (DLM)		√	√	
Linezolid (LZD)		√		
Pretomanid (Pa-824)		√	(√)	On watch-list DR-TB LTBI
Formulations: All dispersible scored				

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Implementation consideration for the Short-term list

RIF	• Data available: can increase efficacy and lead to regimen shortening, • Single rather than FDC as ratios will change across weight bands (for "top up") • Ideal dose of a dispersible tab to be determined
RPT	• Same rationale as for RIF for single need • Formulation dispersible (potentially scored) – dose TBD on PK study
BDQ	• Group A WHO DR-TB guidelines, recommended from age 6*
CFZ	• Group B WHO DR-TB guidelines
DLM	• Group C WHO DR-TB guidelines, recommended from age 3**
LZD	• Group A WHO DR-TB guidelines • Syrup (very expensive); 150mg dispersible tablet in development
Pa	• PK and safety studies underway

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Watch list	DS-TB	DR-TB	LTBI	Remarks
RHZLfx FDC	√			If SHINE not successful and TBTC study 31 LFX arm successful
RHZE FDC	√			To address barriers to the use of ethambutol
Telacebec (Q203)		√		Currently phase IIa
Sutezolid (PNU-100480)		√		Currently phase IIa
Delpazolid (LCB01-0371)		√		Currently phase IIa
OPC-167832		√		Currently phase IIb/IIa
Moxifloxacin (MFX)		√		Taste-masked

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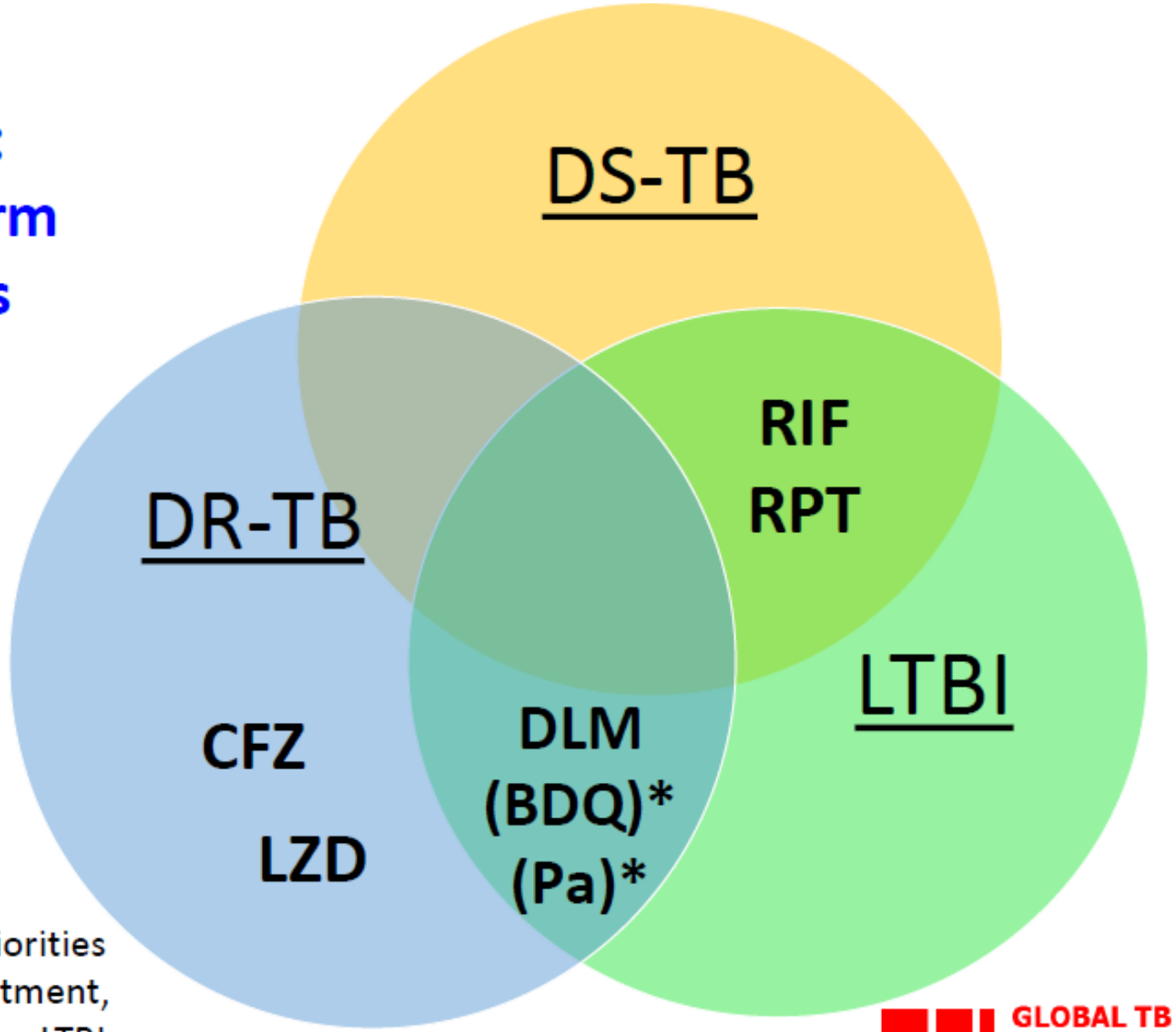
Venn-diagram: short-term priorities



* BDQ and Pa: Short-term priorities for DR-TB treatment, on watch list for LTBI

GLOBAL TB PROGRAMME

How do we focus our efforts and maximize impact?

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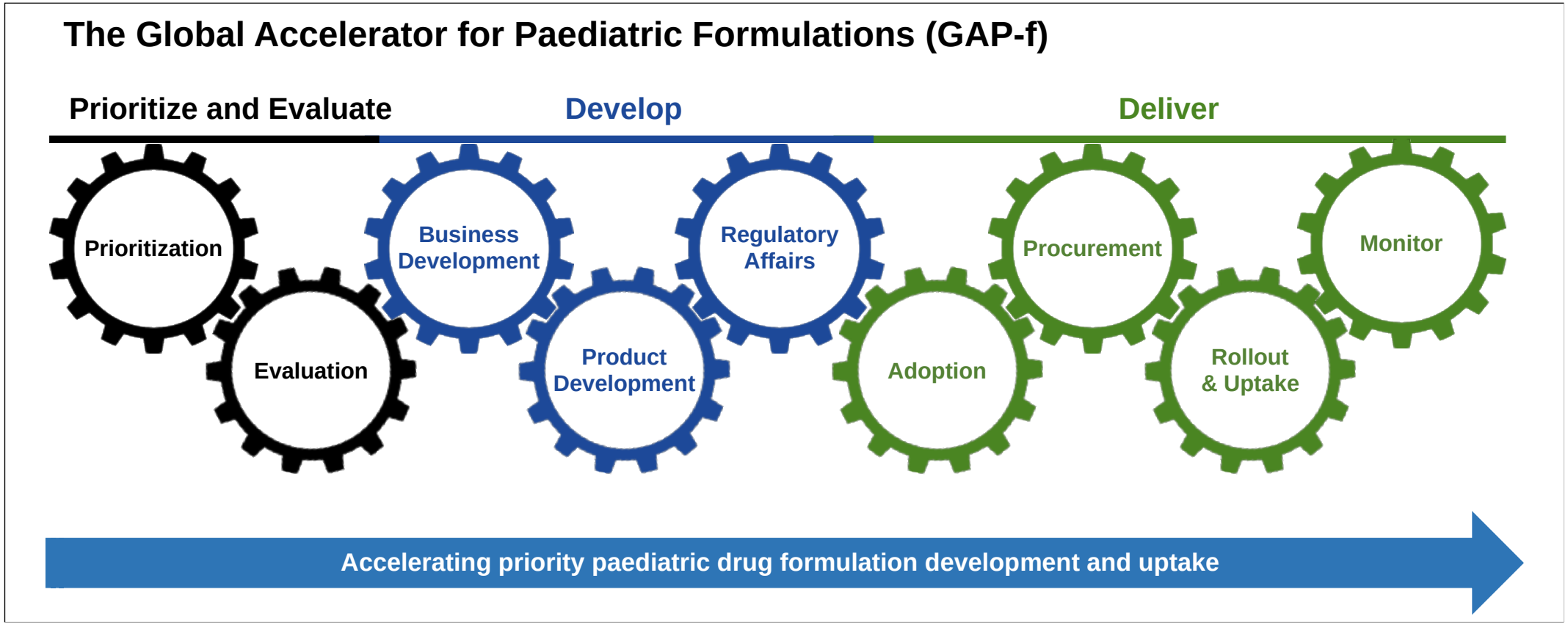
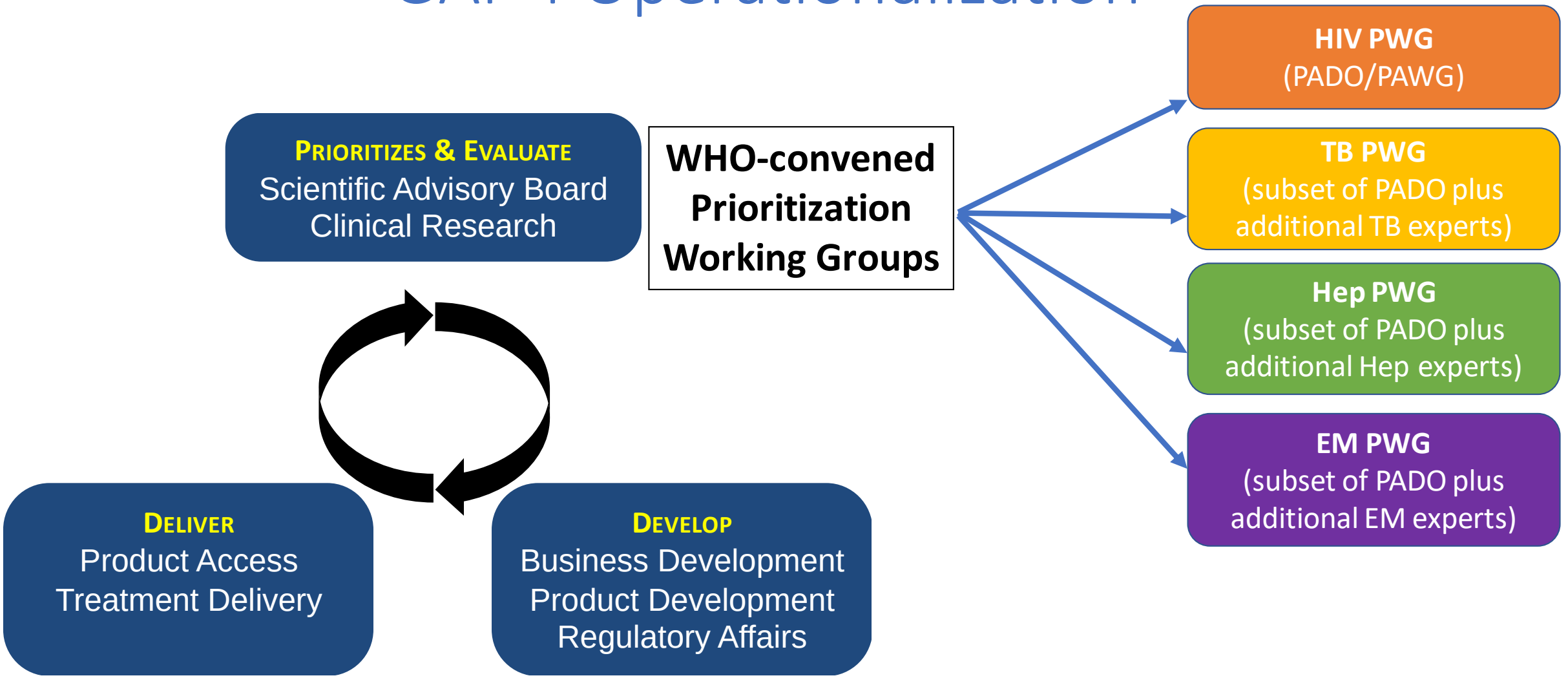
How does this link with the broader work on paediatric medicines?

GAP-f: Formal collaboration across sectors to ensure accelerated development and uptake



A collaboration platform supported by an innovative financing mechanism that promotes a faster, more efficient and more focused approach to paediatric clinical and formulation development and introduction.

GAP-f Operationalization

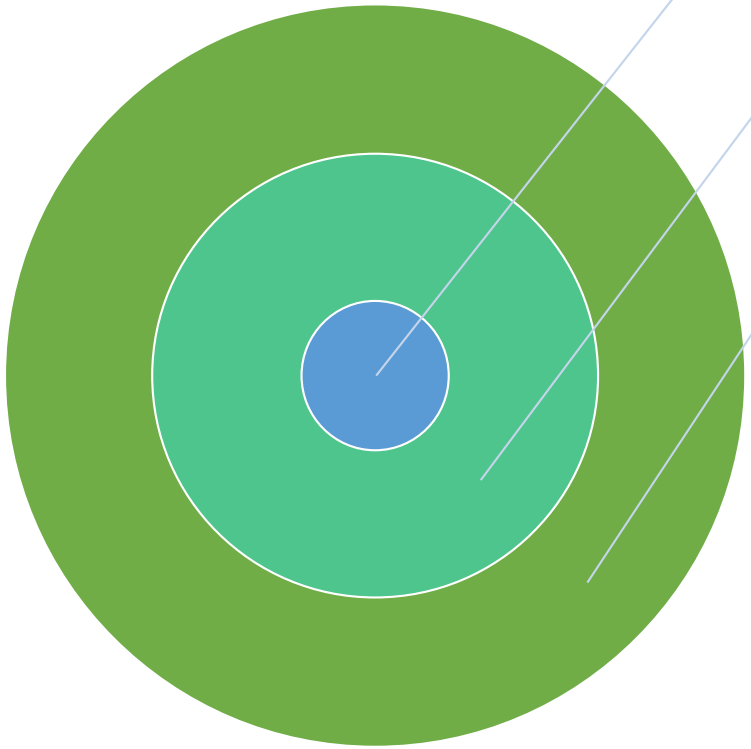


GAP-f will be implemented via key stakeholders operating in the different disease areas and building as much as possible on existing platform, ongoing work and

PADO TB (PWG for TB)

- Meeting every two years
- Mid-term review to assess implementation, issues and internal prioritization of the PADO priorities
- Dissemination of PADO priorities via: webinars, peer-review papers
- Ensuring that PADO priorities are captured in EOI and ERP as soon as dosing and ration of the formulation is identified
- Active reach out to regulators and industry to input PIP/PSP design as well as facilitate rapid completion of those

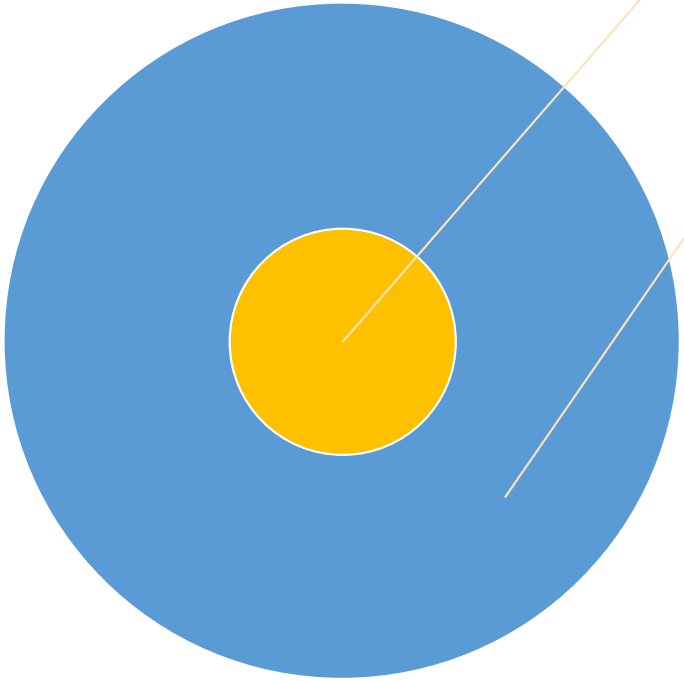
Prioritization working group will work as best fit the technical area



Paeds R&D clinical and PK experts interest in drug development

PAWG clinical, PK, programmatic expertise on Paeds and PLW

PADO includes partners and MOHs and ad hoc experts



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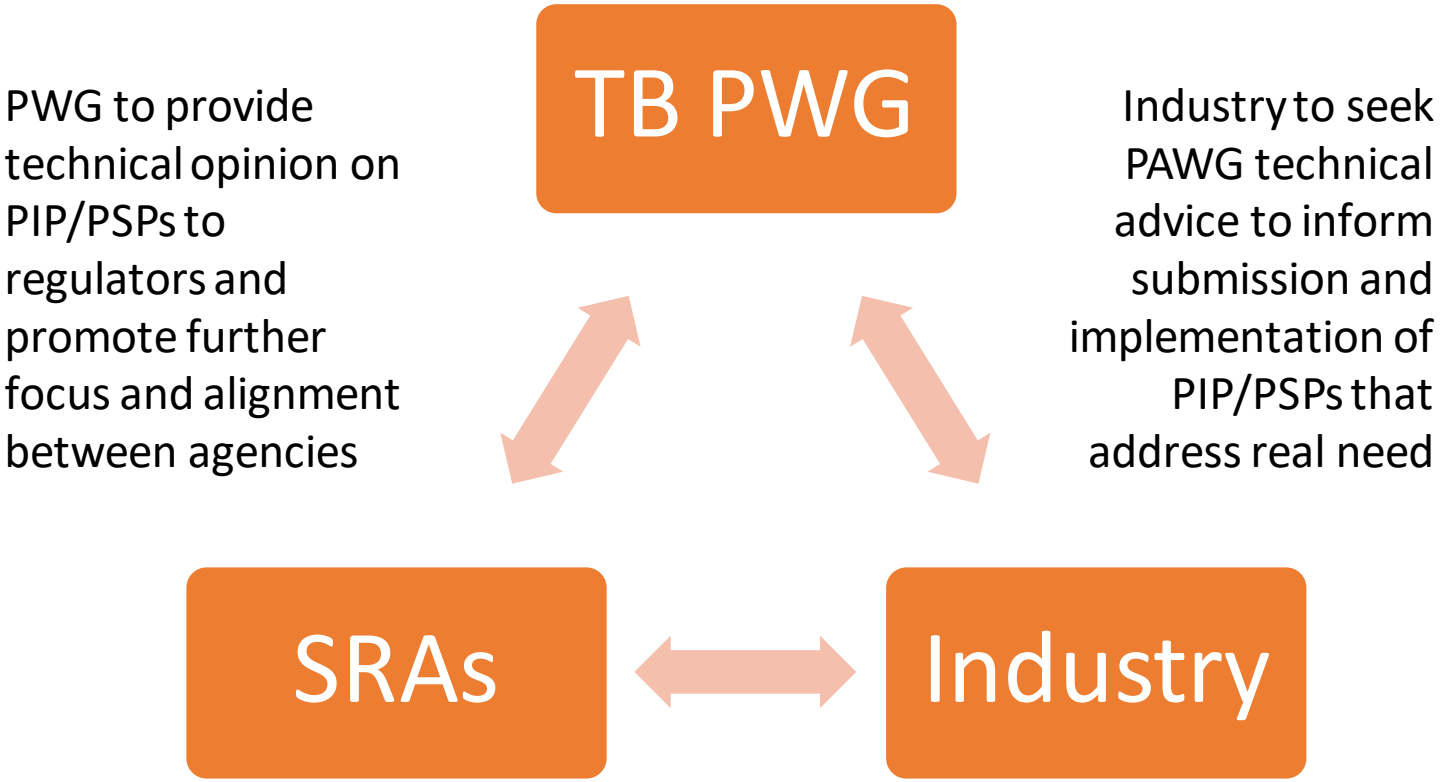
Closing the loop on paediatric development plans



Better paediatric development plans completed and approved more quickly

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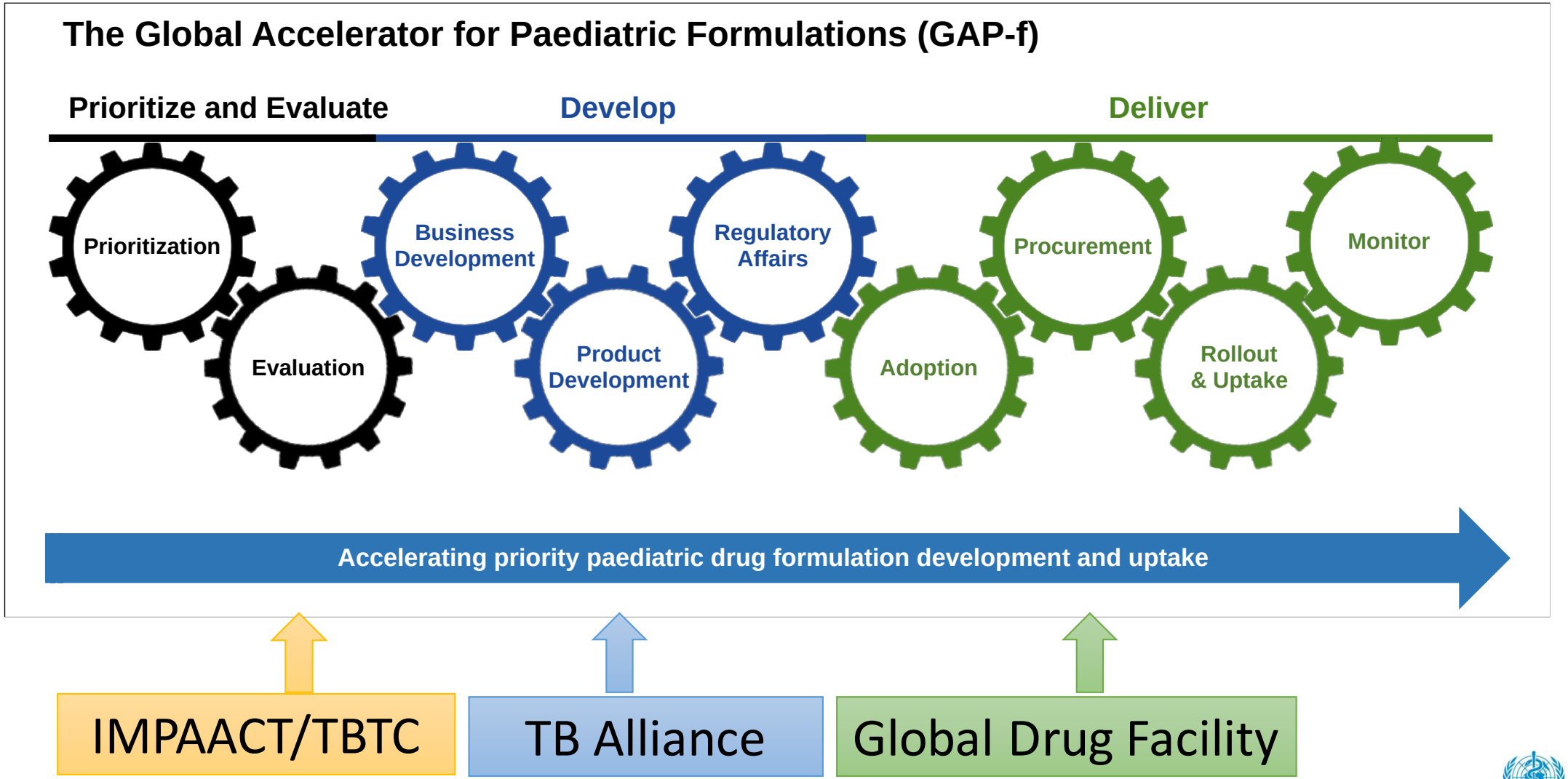
TB partners landscape



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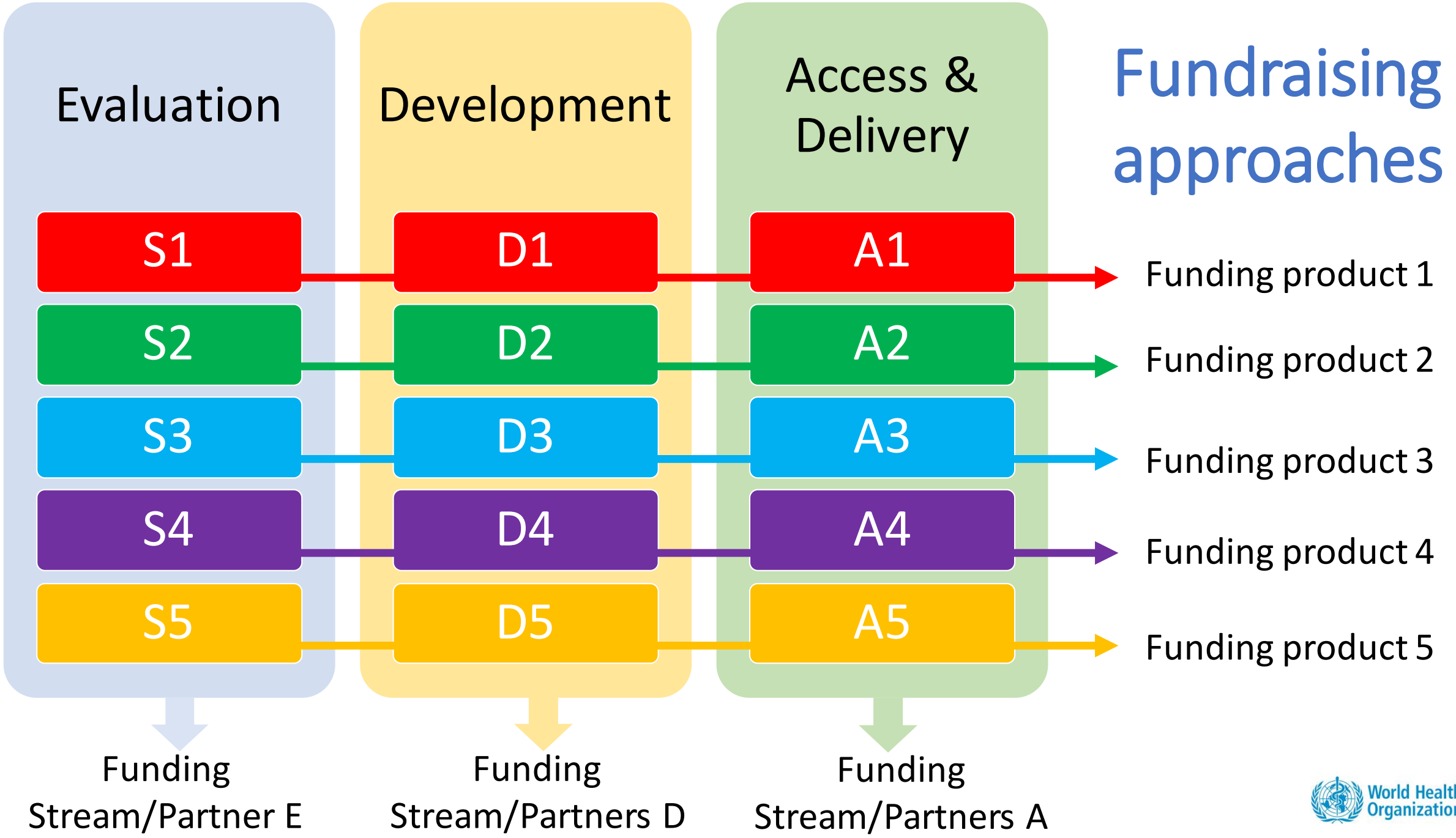
Fundraising approaches



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Catalysing a strong political support and leverage it to generate commitments

- Next meeting will include TB as a new area of focus
- Meeting to be held in February 2020

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THANK YOU

https://www.paediatrichivactionplan.org/

http://www.who.int/hiv/pub/research-dev-toolkit-paediatric-arv-drug-formulation/en/

http://gap-f.org/

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