



Welcome to the eighth issue of *Evidence Notes*. This article is the second of three focusing on the Adaptive Pathway Initiative. Currently the pharma industry is investing heavily in developing the necessary infrastructure and capability to effectively harness real-world (RW) data and **this article** describes the latest publicly available thinking by the regulators and other key stakeholders on Adaptive Pathways, and the role of RW data therein (as a reminder, Part 1 of this series examined the place of PCTs in pre-approval medicine development, and a future Part 3 will examine the actual impact of RW data on regulatory & HTA decision making). As with all our Evidence Notes, the aim is to provide a brief readable summary, rather than a lot of technical information. References are provided for further information.

## The Role of Real-World Data in the Adaptive Pathways Initiative

The Adaptive Pathways (AP) initiative, launched by the EMA in 2014, is a prospectively planned approach to medicine development based on 3 core principles<sup>1, 2, 3, 4</sup>:

1. "Approval" is not a single event but is iterative to either (a) expand the target population from an initial approval in a well-defined patient population with high medical need, or (b) progressively reduce uncertainty after a conditional approval based on surrogate endpoints, early time points, or a smaller population sample.
2. Real-world (RW) data is used to supplement traditional clinical trial data (typically RCTs)
3. All relevant decision makers across the life-span of the medicine are involved in development plan discussions (e.g. patient-groups, HTAs etc.)

The ultimate aim of AP is to allow patients who are most likely to benefit from a new medicine to have access as soon as possible whilst maintaining patient safety, and at the same time allowing for generation of RW data to help inform future label expansion.<sup>1, 4, 5, 6, 7, 8</sup>

Whilst RCT studies are the gold standard for addressing efficacy in a defined population, RW studies are more generalizable than RCTs and are therefore better able to address "effectiveness" in the broader patient population. But because they are usually conducted post approval, at present,

HTAs have to rely at present on RCT data alone to make their initial decisions, rather than on effectiveness and cost-effectiveness vs existing standard of care in the real world<sup>9</sup>. As a consequence, patients do not always receive timely access to new medicines. For example, some have argued that an AP approach might have resulted in the earlier availability of UniQure's gene therapy Glybera (for lipoprotein lipase deficiency) available sooner if a narrower group of patients had been targeted rather than the original broader population<sup>10, 11</sup>. Thus, identification of appropriate patient subgroups that are more likely to respond to a particular medicine is also important.

The type and time course of evidence generation for the current regulatory scenario vs AP is illustrated by Eichler et al 2012 (see Figure 1, page 432 – we were unable to reproduce here due to copyright issues)<sup>5</sup>. In the current scenario most patients pre-license are enrolled in RCTs. Once approval is received, the treated population expands rapidly but few patients are observed or formally monitored. In AP there may be fewer patients in pre-license RCTs and an initial license may occur earlier. Subsequent to this initial license, a significant proportion of patients would contribute to RW evidence generation. Thus, expansion of the treated population would grow more slowly and would be more evidence-based<sup>5</sup>. The AP approach would, however, be similar to the current scenario in using existing EU regulatory processes (including scientific advice, conditional approval etc.) and, importantly, would not seek to alter the required standards for evaluating risk/benefit<sup>1</sup>.

To understand the practical implications, the EMA began a pilot project (March

2014)<sup>1</sup>. From 62 applications in a wide range of therapy areas, 18 were selected for exploratory, informal and non-binding "safe harbour" discussions between EMA, HTAs and patients. By the end of the pilot, 6 (covering oncology, haematology, anti-infective and cardiovascular) had received formal parallel EMA/HTA scientific advice. In these 6 cases, the stakeholders reached an agreed development plan where, in addition to the 3 core principles described above, the following criteria were satisfied: reliable surrogate endpoints existed, the population to be initially treated could be clearly identified, evidence generation was a challenge (e.g. rare cancers, infectious diseases, Alzheimer's disease, and degenerative diseases), and there was a reliable post authorisation plan to record long-term endpoints.

AP was not considered appropriate for medicines in diseases where there is not an unmet need (e.g. effective treatments already exist), development programmes that did not allow scope for expansion and iteration, or when no changes to the plan could be effected (e.g. late stage development programmes)<sup>1</sup>.

The use of RW data to complement RCTs is perhaps the defining feature of AP and Table 1a and 1b shows the RW data requirements considered important for an AP route as well as the RW proposals accepted for "safe harbour" discussions<sup>1</sup>.

However, the RW plans were considered an area of major weakness in the submitted proposals. Whilst EMA accept the methodological difficulties with generating RW data, the majority of the plans were "vague"; had "insufficient detail" on the extent to which efficacy



could be confirmed or augmented by RW data or on the practical elements for implementation, and were lacking in “a critical discussion on the quality, potential for bias, and reliability of the data acquired in the post authorisation setting, and their suitability for regulatory and HTA purpose...”<sup>11</sup>. So, this remains an area of significant opportunity for those with robust RW data plans, and studies such as the Salford lung study (see Bridge Medical Evidence Notes 7) could provide a useful template<sup>9</sup>.

Establishing value relative to existing treatments in RW studies is also crucial and is even more important in AP than in conventional regulatory routes. Simply providing statements regarding the need, burden of disease, cost or the shortcomings of existing treatment is insufficient. There will need to be detailed plans on how an added benefit over current therapy will be demonstrated (e.g. to show reduction in health care costs/resource use etc.)<sup>1, 12</sup>.

Publicly available information on the development plans for the projects evaluated in formal scientific advice is limited and Table 2 summarises the available information for 4 of the 6 projects. In their report, the EMA omitted much of the detail about these development plans for confidentiality reasons, a decision which has drawn criticism from IQWiG (German Institute for Quality and Efficiency in Healthcare)<sup>13</sup>.

Table 1a:

**RW Data Requirements for AP and RW Proposals Accepted**

RW data requirements considered important for AP
Define purpose of RW data collection (regulatory, HTA, or both); why is this proposed and necessary, instead of, or in addition to an RCT?
Specify type and timing of RW data (prospective disease registries; follow-up drug registries)
Critique quality of RW data, particularly in case of utilisation of existing disease registries, & fitness of data for intended purpose; Ensure reliable, clear-cut and actionable RW endpoints exist
Set up milestones for results checking & development of scenarios depending on emerging level of efficacy data (e.g., heavier reliance on post-authorisation RW data may be possible for a higher level of efficacy)

Table 1b:

RW Proposals Accepted for “safe harbour” discussions
Use of existing disease registries to identify natural history of disease, current standard of care, resource utilisation, adherence to treatment
Single arm studies for rare diseases compared with outcomes and time-points inferred from disease registries
Open label salvage studies in patients with no therapeutic options remaining, for expansion of the indication
Collection of efficacy and safety data from early access/compassionate use programs to supplement RCTs in small populations
Post-authorisation drug registries for effectiveness, long-term outcomes, drug utilisation, Patient Reported Outcomes (PROs), time to treatment failure, diagnosis confirmation
Linking drug registries to risk-sharing schemes for reimbursement (pay-per-performance, annuity payments)
Expansion of the indication based on a mixture of disease registries and compassionate use data (for rare, severe diseases, where RCT data were available for less severe forms of the disease)
Post authorisation studies to investigate biomarkers’ (or other subpopulation selection criterion) status of an all-comer population
Investigation of non-serological outcomes for vaccines.

Table 2: Development Plans for 4 of the 6 Projects Selected for the AP pilot<sup>1, 14-18</sup>

Therapy/Company	Disease Area	Development Plan
Lentiglobin BB305 (gene therapy)/ Bluebird Bio <sup>14</sup>	Beta-Thalassemia Major	Initial conditional approval in adults & adolescents will be based on the totality of clinical data, in particular reduction in transfusion need, from 2 ongoing studies - HGB-204 (Northstar Study, global phase I/II) and supportive HGB-205 (single centre, France). These will provide the basis for initial labelling and the value proposition. Conversion to full approval subject to: 2 OL studies (HGB-207, adults/adolescents; HGB-208, paediatric subjects; n=15 in each); supportive long-term follow-up data; and “real-life” post-approval monitoring data. This information will be used by regulators, HTA bodies & payers in their assessment & decision making. <i>“It is of interest to all parties, including patients, that a prospective discussion takes place on the data elements &amp; design of long-term evidence generation to collect relevant &amp; high quality data”</i>
PLX-PAD (Placenta-based cell therapy)/ Pluristem Therapeutics <sup>15</sup>	Critical limb ischaemia (CLI)	An initial single Phase II/III randomised, D/B, P/C trial of PLX cells in a subgroup of patients with severe CLI (n=250); two successful Phase I studies in CLI
IMCgp100 (T cell receptor biological)/ Immunocore <sup>16</sup>	Metastatic uveal melanoma	Seek conditional approval on the basis of a Phase IIa study in late stage melanoma and long term follow up data; one successful Phase I study
F901318 (systemic orotomide antifungal)/ F2G <sup>17</sup>	Invasive Aspergillosis	Seek initial approval on the basis of a Phase IIB RCT

D/B = Double-Blind; P/C = Placebo-Controlled; OL = Open Label



Table 3: Other Learnings from the AP pilot

Additional Essential Elements for AP
<ul style="list-style-type: none"> <li>Prospective planning essential across the product life span</li> </ul>
<ul style="list-style-type: none"> <li>Wide consultation with all relevant bodies (e.g. regulatory, HTA, patients, and possibly payers)</li> </ul>
<ul style="list-style-type: none"> <li>Development plans should make use of robust mechanisms for post-authorisation data to ensure close monitoring of a medicine's benefits and risks once it is on the market</li> </ul>
<ul style="list-style-type: none"> <li>Other preconditions include:                             <ul style="list-style-type: none"> <li>The setting of checkpoints across the development pathway to revise &amp; adjust the programme</li> <li>The medicine can only be prescribed to the patient population for which the benefit/risk has been demonstrated</li> <li>The ability to arrange managed entry agreements and entry and exit strategies if these are considered relevant by the concerned stakeholders</li> </ul> </li> </ul>

Further guidance to help identify suitable candidates for AP has been developed in the EMA updated guidance (see Figure 1)<sup>12</sup> and other learnings from the pilot are captured in Table 3<sup>1</sup>.

There remain, however, significant criticisms of the AP approach including concerns about: a perceived lowering of evidentiary standards<sup>13, 19-22</sup> (denied by EMA<sup>23</sup> & others<sup>24</sup>), surrogate outcomes<sup>23, 25</sup>, operational issues<sup>1, 25</sup>, the timing of paediatric studies<sup>1</sup>, legal authority<sup>26</sup> and potential erosion of exclusivity and patent protection periods<sup>27</sup>. It is outside the scope of this article to cover all these points but, given the importance of RW data as a unique feature of AP, Table 4 provides a summary of the relevant key RW data concerns (point) together with available responses (counter-point).

Some clear next steps for further consideration have been noted such as: input from a broader range of HTA's, patients, healthcare professionals and, where relevant, payers; understanding the strengths and limitations of RW data and the development of suitable methodologies by working with other projects (e.g. Innovative Medicines Initiative, GetReal etc.); developing early health economic models; and allowing additional pre-submission meetings for small/medium enterprises<sup>1</sup>. A workshop is planned (December 2016)<sup>29</sup> to further discuss AP and its implications.

Figure 1: Product Eligibility for AP

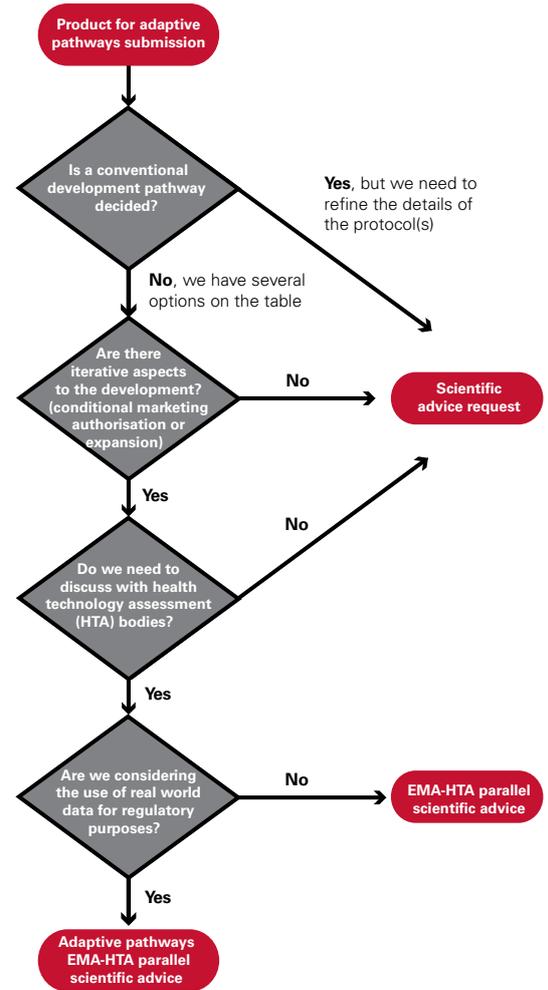


Table 4: Key Real-World Data Issues with Adaptive Pathways: Point vs Counter-Point <sup>1, 13, 20, 23-25, 28</sup>

POINT	COUNTER-POINT
IQWIG criticised EMA for having “no concept as to how RW data can be used after drug approval to allow drawing reliable conclusions on benefit and harm”, and for not providing their own proposals on how to use these data. The weakness of RW plans was described by IQWIG as “extremely sobering”. <sup>13</sup>	EMA “reject IQWIG’s conclusion about the limitations of RW data.” Methodological challenges to the use of RW data are recognized and the pilot was intended to be “a learning exercise.” The weakness of submitted plans was “not a judgement of the usefulness” of RW data and, “in several instances, EMA advised companies on what kind of real-world data and methodologies of analysis would be expected.” <sup>28</sup>
There is an “enormous body of evidence” calling into question the reliability of observational data <sup>20, 25</sup>	RCT (as well as observational) studies may produce non-reproducible or contradictory results. In AP, RW data would be used to complement RCTs and <i>all</i> the evidence, (observational & RCT data) would be used to inform decision-making. But “inferences based on observational studies may need to be more circumspect”. <sup>23</sup>  By adding RW data earlier in the process, more relevant evidence will be provided for non-regulatory decision-makers, such as HTA bodies and payers. <sup>24</sup>
Observational studies cannot be relied on to compensate for weak evidence of benefit. <sup>20</sup>	Rigorous pragmatic approaches to observational studies which preserve the strengths of randomisation, may complement RCTs by addressing their lack of “generalisability” in cases where there is robust evidence of efficacy. <sup>20</sup>
For many products AP plans will be required when it is not yet known if the product will prove effective. Thus, early in development there is limited data from which to develop detailed RW plans or value proposition strategies. <sup>1</sup>	Different scenarios should be planned based on different efficacy levels, and the amount & type of data available at various milestones. E.g. if there are compelling early data with potential for substantial improvements to patient care a more accelerated licensing and re-imburement strategy may be possible; in case of more marginal results an RCT based approach may be required. <sup>1</sup>



## Conclusion

AP is an iterative medicine development process in areas of high unmet need which allows those patients most likely to benefit to have access to a new medicine as soon as is safely possible. At the same time, the generation of early RW evidence is “a unique feature... that no other development setting foresees at present”<sup>23</sup>. Although challenges to the use of RW data are well recognised, the AP process would ensure the plan is subject to methodological expert review and multi-stakeholder advice.

EMA categorically dispute that AP lowers evidence standards and increases risk to patients. The idea, they argue, is to increase evidence in a staggered way “with continuous learning over the lifespan of a product.”<sup>18</sup> Whilst this approach may result in a greater degree of initial uncertainty, they do not accept it necessarily implies increased risk.<sup>4</sup>

AP is in its early stages of development and EMA recognise that this is an emerging concept that will evolve as more is learned from the experiences of those products in the pilot and as more potential medicines are assessed via AP.<sup>30</sup>

Further information on this subject can be found in the references provided.

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