Regulatory Refresh: How the regulatory system should be a driver for change

N1C Annual Meeting, Montreal

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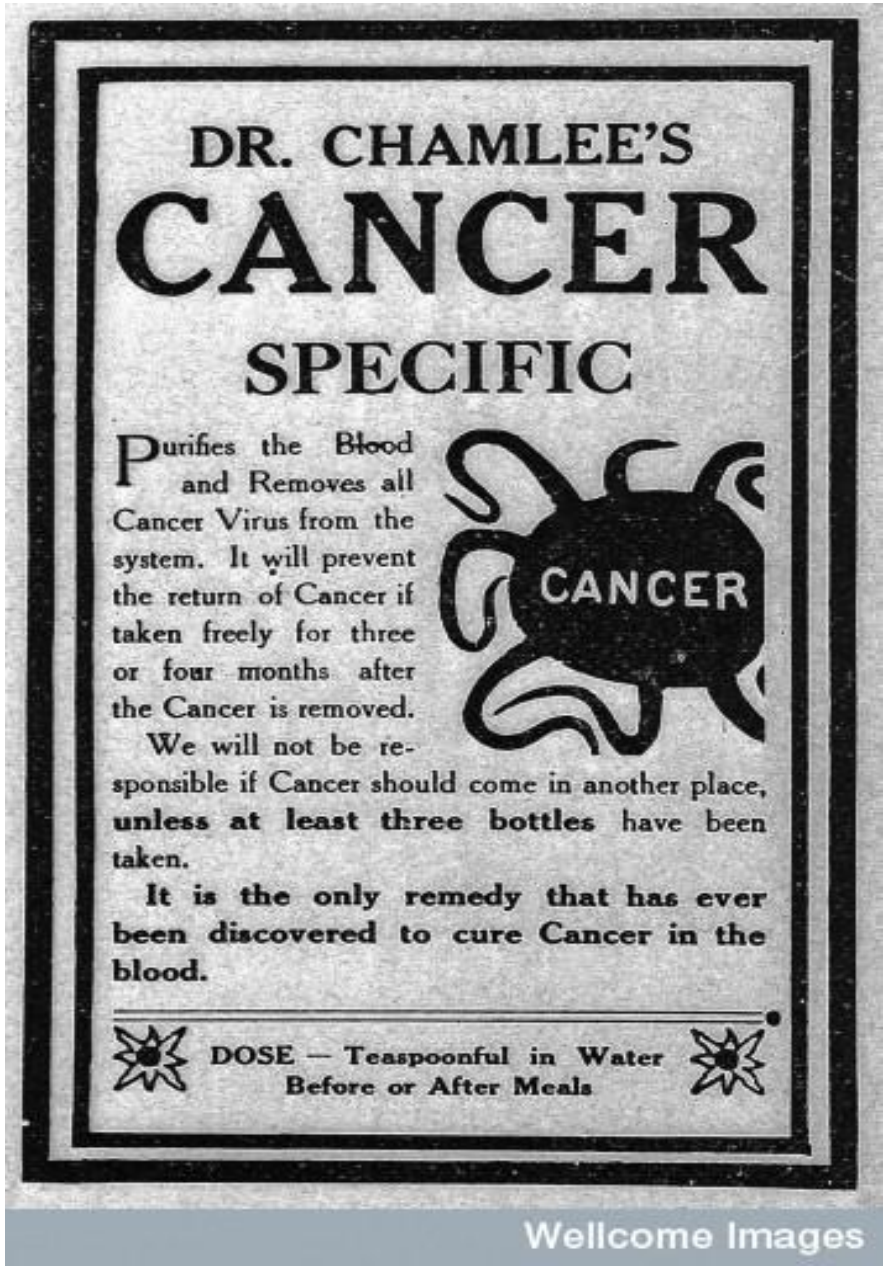
Disclaimer: the context of this presentation, the views expressed are mine and do not necessarily constitute ABPI policy

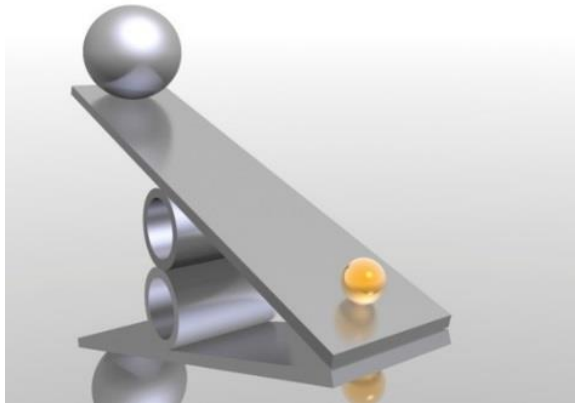
Why we need drug regulation



- Before the era of drug regulation, there was no formal mechanism to ensure medicinal products were of high quality, safe and efficacious
- In 1920s USA, Dr Chamlee's specific claimed to be the only remedy that had ever been discovered to cure cancer in the blood!
- Claims a Pacific island shrub produced "cures"
- Future chemical analysis showed that no active anticancer ingredient was present
- Advertisements like the one opposite were common and deceived vulnerable patients

Regulatory environment

- The regulatory environment is key to protect public health and attracting inward industry investment
- The pharmaceutical field of life sciences and medicine development has become increasingly global, multinational firms must make informed and often challenging decisions about where & when to locate their activity
- National regulatory frameworks are a key consideration when these decisions are made
- Vital for regulators to provide a globally competitive approval system that is:
  - Proportionate and committed to ensuring patient safety
  - Attractive to inward investment and research and development



Some trends in Regulatory Science

- Patients are increasingly well informed about their disease, existing treatment options, novel developments on the horizon, and share information with others across regions
  - Need to ensure meaningful patient engagement, how to do this well?
- Scientific progress is facing rapid development with impressive achievements in medicine, pharmacology, basic science, and technical disciplines. With this we also face several novel challenges inherent with the possibilities that technology can provide (e.g. whole genome sequencing, AI, drug-device combinations, gene editing etc)
  - How can Regulators and regulation keep up? What does proportionate regulation look like?
- Regulatory bodies are facing challenges with decisions to be made faster with less data so as not to delay the availability and access to newly developed treatments

The rise of the small population – when rare becomes common

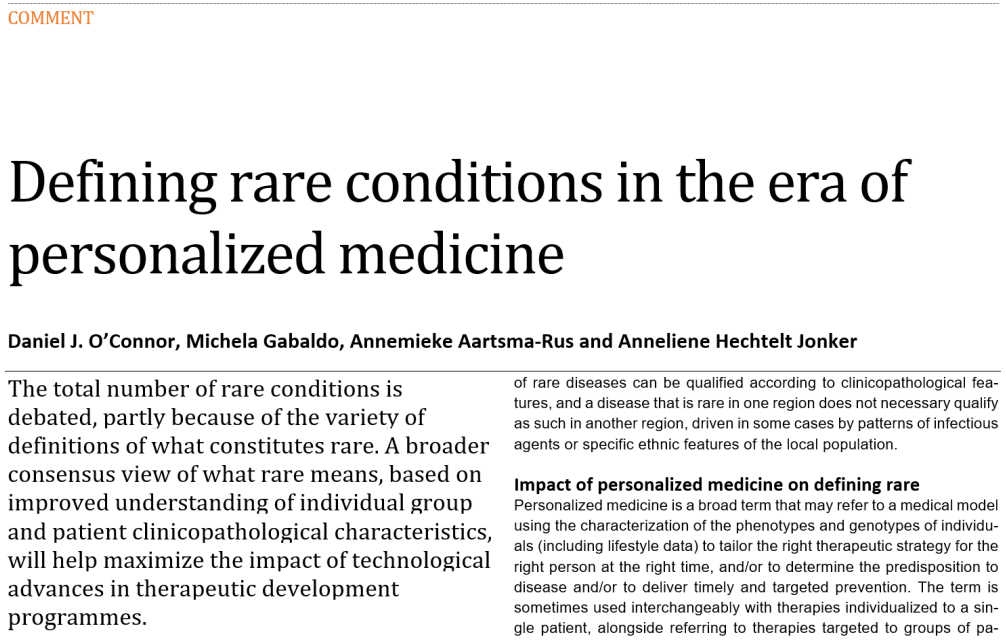
The rise of the small population – when rare becomes common

- There are estimated to be 6000-10000 traditionally described rare diseases – only 5% have a therapeutic option despite many being life limiting and/or seriously debilitating
  - ➢Huge unmet need – current model is not delivering access at pace or scale

- There is no common global agreement on the impact and widespread application of advances in molecular sciences and pathology on the definition of rare

- In era of personalised medicine:
  - Subsetting of common conditions
  - Shared molecular entity conditions

    (basket - disease agnostic)
  - Subsetting of rare conditions



COMMENT

Defining rare conditions in the era of personalized medicine

Daniel J. O'Connor, Michela Gabaldo, Annemieke Aartsma-Rus and Anneliene Hechtelt Jonker

The total number of rare conditions is debated, partly because of the variety of definitions of what constitutes rare. A broader consensus view of what rare means, based on improved understanding of individual group and patient clinicopathological characteristics, will help maximize the impact of technological advances in therapeutic development programmes.

of rare diseases can be qualified according to clinicopathological features, and a disease that is rare in one region does not necessary qualify as such in another region, driven in some cases by patterns of infectious agents or specific ethnic features of the local population.

Impact of personalized medicine on defining rare

Personalized medicine is a broad term that may refer to a medical model using the characterization of the phenotypes and genotypes of individuals (including lifestyle data) to tailor the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention. The term is sometimes used interchangeably with therapies individualized to a single patient, alongside referring to therapies targeted to groups of pa-

How do we currently define rare?

- Numerous and overlapping regulatory definitions – traditionally described with specific clinical features - generally defined by low prevalence

- An operational description of rare diseases has been proposed by Rare Diseases International and a panel of experts, in collaboration with the WHO

  - *A medical condition with a specific pattern of clinical signs, symptoms and findings that affects fewer than or equal to 1 in 2,000 persons living in any World Health Organization-defined region of the world*

- The description does not address the role of personalised medicine

What is a rare disease?

How many people live with a rare disease?

Why do Persons Living with a Rare Disease and their families require specific attention?

Flexibility in the FDA approach to orphan drug development

Nina L. Hunter, Gayatri R. Rao and Rachel E. Sherman

Scientific advances, in combination with government incentives and commercial opportunity, have fuelled strong investment in orphan drugs, resulting in many innovative therapies.

COMMENT

Defining orphan conditions in the context of the European orphan regulation: challenges and evolution

Daniel J. O'Connor[1,12], Maria E. Sheean[2,3,12], Matthias P. Hofer[2,12], Stelios Tsigkos[2], Segundo Mariz[2], Laura Fregonese[2], Kristina Larsson[2], Virginie Hivert[4], Kerstin Westermark[5], Frauke Naumann-Winter[6], Violeta Stoyanova-Beninska[7], Ingeborg Barišić[8], Giuseppe Capovilla[9], Armando Magrelli[10] and Bruno Sepodes[11]*

The definition and acceptability of an orphan condition is pivotal for the assessment of European orphan medicinal product designation applications, and consequently the eligibility for incentives. Here, based on the experiences of the Committee for Orphan Medicinal Products, we discuss how to define orphan conditions in the context of the European regulatory framework.

Defining rare conditions in the era of personalized medicine

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Subsetting in common diseases

- Molecular research tools, knowledge on disease aetiology and pathology has substantially increased – dynamic and fast-moving field of diagnostics

- Common prevalent diseases are increasingly being redefined based on biomarkers and other genetic characteristics

- Many of these subsets have low numbers of patients – and share many of the same challenges when considering research involving small populations

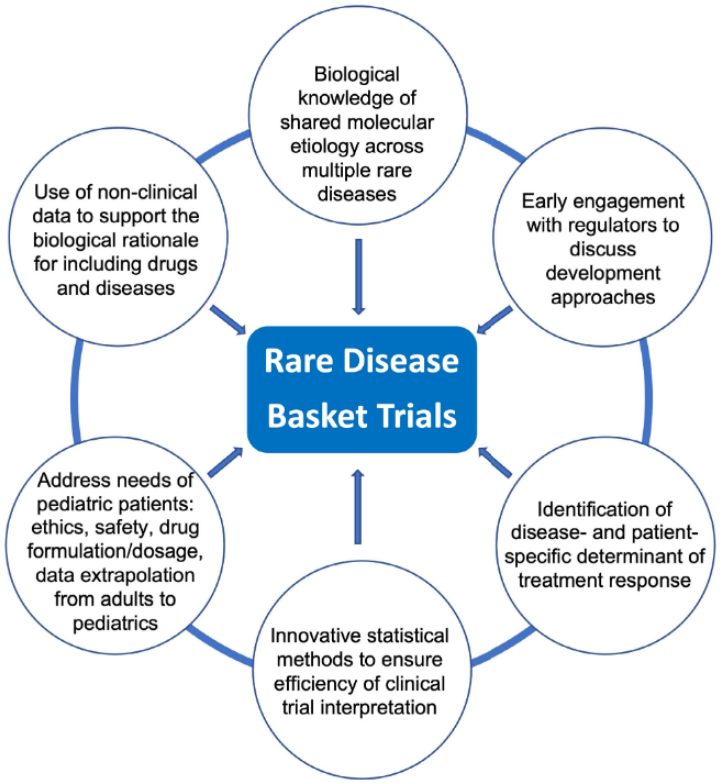
- Affects the policy provisions and the total number of rare conditions

Shared molecular entity conditions

- Grouping patients with rare diseases based on the same underlying molecular aetiology has the potential to identify groups of diseases likely to respond to the same therapeutic agent:

  - Mutations in the same gene, the same type of mutation affecting different genes, or mutations in different genes affecting the same molecular pathway

- Could allow innovative approaches that may greatly increase the number of patients gaining access to clinical trials and experimental treatments with the potential to accelerate drug development



Review

OPEN ACCESS

EMBO Molecular Medicine

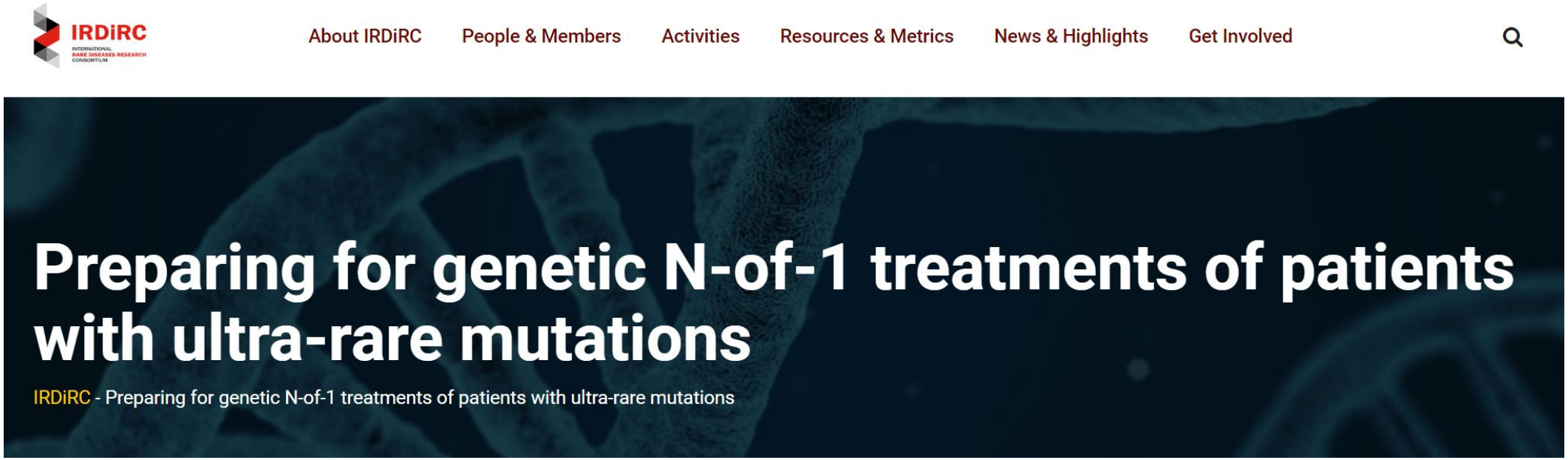
Targeting shared molecular etiologies to accelerate drug development for rare diseases

Galliano Zanello[1,†], Macarena Garrido-Estepa[2,†], Ana Crespo[3], Daniel O'Connor[4], Rima Nabbout[5], Christina Waters[6], Anthony Hall[7], Maurizio Taglialatela[8], Chun-Hung Chan[9], David A Pearce[9,10], Marc Dooms[11] & Philip John Brooks[12,*]

Subsetting in rare conditions

- In some rare genetic diseases, subsets of specific pathogenic variants exist - these subsets can be extremely small or the variant may affect just one person

- Need for N of 1' individualised precision medicine approaches and proportionate and innovative approaches that recognise the unique challenges would help advance the field



Why is it important that we have a shared understanding of rare?

- Improve recognition of the unique challenges in the community and raise the visibility of the burden of being a patient with a rare disease
- Facilitate collaboration and creation of shared goals and opportunities
- Influential in terms of the type of clinical development programme that can be conducted for evidence generation
- Helps drive forward policy provision to aid and facilitate small population research
- **Harmonised regulatory systems are crucial for accessing incentives and aligning requirements, avoiding duplication and replication**

Regulatory Refresh: How the regulatory system should be a driver for change

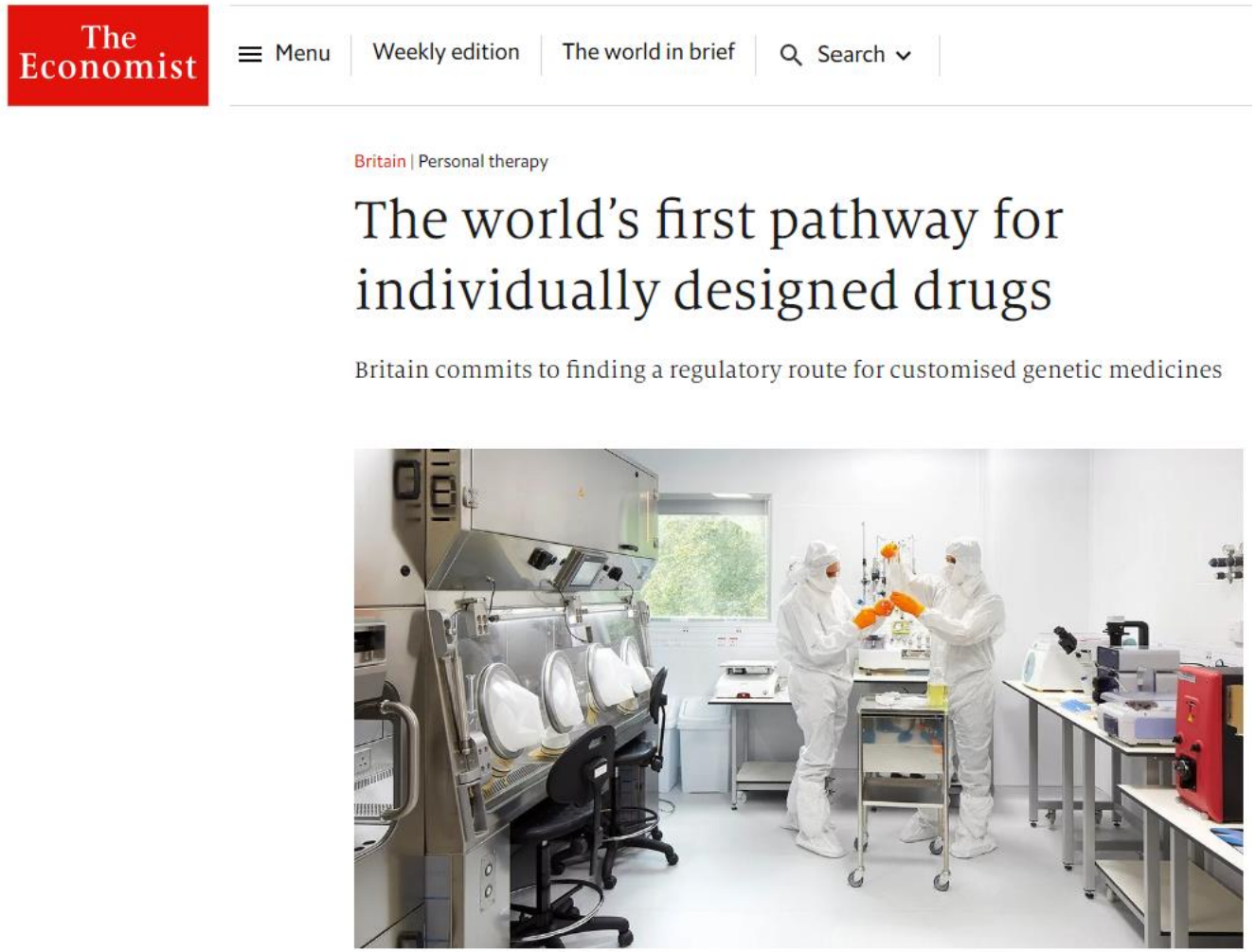
Subsetting in rare conditions

- Increasingly science is not the limiting factor for access to individualised medicines

- Therapeutic window – need to link the patient to a therapeutic intervention early

- Urgent need to develop a N of 1 / individualised precision medicine pathway, utilising proportionate and innovative approaches that recognise the unique challenges

- The *Rare Therapies Launch Pad* was founded to help patients access individualised medicines at scale in a sustainable way



Rare Therapies Launch Pad (RTLP) – Opportunity to Innovate

Rare Therapies Launch Pad (RTLP)

- Announced in the Autumn Statement 2023 – pilot programme to develop a new pathway

- Urgency to develop new approaches due to the high unmet medical need and the mismatch between what is technically feasibly with 21st century science and what is currently available

- Develop and evolve the pathway through an initial focus on antisense oligonucleotides (ASOs) in small numbers of children with fatal and life-threatening brain conditions

- Aims include:
  - Identify sustainable and scalable approaches to delivering individualised therapies
  - Establishing a proportionate regulatory pathway – *condition and treatment modality agnostic*
  - Create a framework to help establish potential reimbursement

RTLP approach

- Establish a new pathway through collective expertise and safe harbour discussions, initiating a small-scale pilot to address the benefits and challenges, providing a new framework for treating patients

- Key aspects include:

❑ Validating the necessary end-to-end steps, including the associated resources and infrastructure needs

❑ Mapping key stakeholder responsibilities, and conducting a gap analysis of what policy / regulation / legislation can currently flex or be repurposed, and what needs to be amended or established

❑ Fostering an ecosystem that draws on the lessons learned to establish a new sustainable, reimbursable model for delivering individualised medicines to all patients who could benefit from them

❑ Put systems and processes in place to bridge the gap between the patient and the science

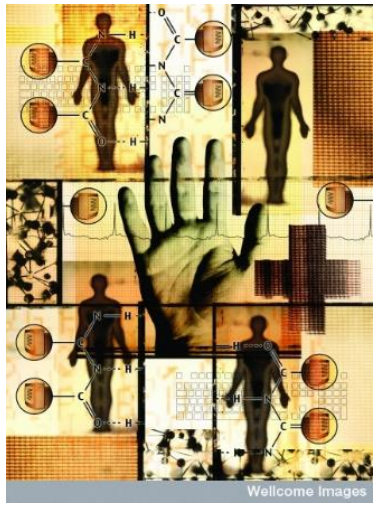
Rare Therapies Launch Pad – Opportunity to Innovate

- Innovative processes and a willingness to think and practice differently are needed to address:

  - How should the regulatory system adapt to a risk proportionate model (clinical trial, marketing authorisation, inspections)?
  - What are the opportunities to extrapolate previous knowledge in the context of ‘platform’ technologies?
  - What solutions can digital technology and AI offer?
  - Could patients enter the pathway through an ‘accredited’ centre with embedded regulatory compliance and arm's length oversight (do and tell)?
  - How can real world evidence collection be leveraged, shifting the paradigm from research to treatment with iterative learning?
  - Regulation needs to link to access - what does the funding and reimbursement aspects look like?

Proportionate regulation

- The regulator is mandated to protect public health, which includes ensuring the regulatory system facilitates and enables access to emerging technologies
- Significant transformation in regulatory process would be the positive driving force for change, recognising the challenges and limitations
- Proportionate regulation does not mean cutting corners, rather an acknowledgement that some of the current steps for regulatory approvals for larger populations could be removed or substituted as they are not fit for purpose or feasible for the individualized medicine approach
- Use new tools, data extrapolation and iterative learning from the real world
- Regulatory science and practice need to evolve to match 21st century science



Problem statements to address

Rare Therapies Launch Pad

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- ***Clinical trials*** are designed to gather research data across population cohorts, which does not fit with the extremely small sample size. However, iterative learning is essential and data can be still be generated and lessons learned using registries and real-world evidence

- ***Compassionate use and 'named patient'*** routes are not designed to deliver access at scale and often place the burden of responsibility solely on the clinician, with little opportunity for system wide data collection. Given the need to create a mainstream pathway for all, these approaches are not feasible

- ***Marketing authorisations or drug licence*** are based on substantive data and risk-benefit decisions for larger populations. Access to individualised medicines cannot be contingent on these approaches given the highly personalised nature and limited evidence generated over long periods of time. A new process is needed that builds on the reproducible nature of platform technologies.

Problem statements to address

- **Safety reassurance** requires rethinking data collection and ensuring proportionate compliance with good regulatory practices (GxP), such as a system of accredited centres providing an accountable process and mandatory central framework for iterative learning from data generated

  - This approach represents a significant evolution in how we generate evidence, consent and monitor patients, and improve treatments within the health system

- ***Risk tolerance:*** We are adopting an already-established risk tolerance from paediatric oncology where debilitating symptoms and loss of life are inevitable without prompt intervention. Risk analysis of treating vs not treating a patient with a fatal genetic condition is comparable with a patient with end-stage cancer where higher-risk experimental medicines are common practice.

Problem statements to address

Rare Therapies Launch Pad

- ***Regulatory/Oversight/Safety reassurance:*** maintaining safety reassurance by shifting toward a more appropriate arms-length regulator where oversight is focused on accredited centres who treat patients within pre-defined and agreed parameters based on prior knowledge and experience, building on regulatory concepts such MHRA Phase I accreditation scheme and ‘do and tell’ processes
  - Access to medicines outside of the accredited centres should be considered research

- ***Data collection:*** Leverage non-clinical safety data from prior products in platform technologies, clinical data collected through a mandated registry system with data review, adopting a position of evidence generation and learning through continuous real world data collection and patient monitoring, in a critical shift from research to treatment

- ***Consent/Ethics:*** Borrowing from the highly individualized, thorough clinician-parent/patient consent process in stem cell/bone marrow transplants & surgery

Reimbusement

- While a transformative change in regulatory oversight is critical to accessing the rapidly maturing technologies available today, the other half of access is dependent upon sustainable reimbursement

- As technology moves us toward many medicines each for small numbers of patients, innovative reimbursement mechanisms are needed

- The RTLP seeks to unblock reimbursement via working closely with industry, the HTA bodies and the healthcare system to determine the barriers

  - Creative thinking needed to create a scalable and sustainable pathway

Summary and next steps

- The RTLP aims to create the infrastructure to make individualised medicines accessible, scalable and sustainable
- The new pathway from diagnosis to treatment and monitoring requires considerable modification of how we think about drug development and access
- Must be visible end-to-end that connects patients to potential treatments, with clear roles and responsibilities
- RTLP is ramping up activities – we don't have all the answers yet – cross stakeholder collaboration is essential – we will test principles through the pilot
- We do have a real opportunity to innovate and a proportionate regulator framework should be at the forefront
- If we are to maximise the benefits of 21st century science, a common global view of rare that incorporates the fast-evolving diagnostic landscape is needed, alongside flexible and pragmatic regulatory and access routes

Thank you

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