Lessons learnt from PETHEMA's RWD research: A clinical perspective

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Abstract

PETHEMA (Programa Español de Tratamientos en Hematología, or, Spanish Program for Treatments in Haematology) a leading cooperative group in haematological research, has increasingly integrated real-world data (RWD) as a complement to traditional clinical trials. RWD research captures information from routine clinical practice, reflecting a broader patient population and enhancing external validity. PETHEMA has conducted impactful RWD studies in acute myeloid leukaemia, acute lymphoblastic leukaemia, multiple myeloma, and bone marrow failure syndromes, notably leveraging large clinical registries and molecular data. Despite challenges such as data heterogeneity, confounding factors, and regulatory constraints, RWD offers essential insights for personalised medicine. Future priorities include improving data interoperability, applying artificial intelligence, and rethinking legal frameworks to balance data protection with scientific progress. PETHEMA's experience highlights the transformative role of RWD in supporting more informed and representative clinical decision-making in real-life haematology settings.

Speaking of PETHEMA

PETHEMA (Programa Español de Tratamientos en Hematología, or, Spanish Program for Treatments in Haematology) is a cooperative research group in medicine comprised of virtually all Spanish haematologists, along with many from Portugal and other Latin American countries. Established in 1972, PETHEMA aimed to generate well-structured protocols to guide the clinical practice of haematology professionals in the field of malignant diseases. Over time, it has evolved into a cohesive and powerful group at the forefront of numerous medical research studies. These include a wide range of clinical trials, but also observational and epidemiological studies, registries, and significant basic translational research related to its focus diseases. PETHEMA operates administratively and legally through its private foundation in Madrid. This foundation currently manages over 80 diverse projects, making PETHEMA the leading non-commercial promoter of clinical studies among Spanish medical societies in Europe. It is surpassed only by three major Spanish public health network hospitals (Table 1).[1] PETHEMA primarily focuses its research activity on multiple myeloma (MM), acute myeloblastic leukaemia (AML), acute lymphoblastic leukaemia (ALL), and chronic lymphocytic leukaemia (CLL), among others.

Real world data (RWD), breaking down the boundaries of cancer research

The first cooperative research among haematologists in Spain began in the early 1970s. The primary tool for this collaboration was the care protocol. This consensus-based document outlined the key guidelines for disease diagnosis and treatment and instructed all participating clinicians to collect a set of essential data on their patients with a specific disease. This data was then sent to a national coordinator, who performed an aggregate analysis of the parameters. This analysis allowed the coordinator to formulate scientific conclusions regarding the patients' response to the pharmacological treatments used. This "virtual circle" process is depicted in the flowchart in Figure 1. This type of research was still very rudimentary, lacking today's standards (no requirement for prior authorisation, no informed consent, no perception of the need for external monitoring), but it had one great advantage: it focused on the universality of patients belonging to a given clinical profile, without incurring any special selection of patients and directly studying real daily clinical practice. In this way, one could say that this type of research was something like a prototype of modern research with real-world data (RWD), where doctors, who had agreed on common diagnostic-therapeutic procedures,

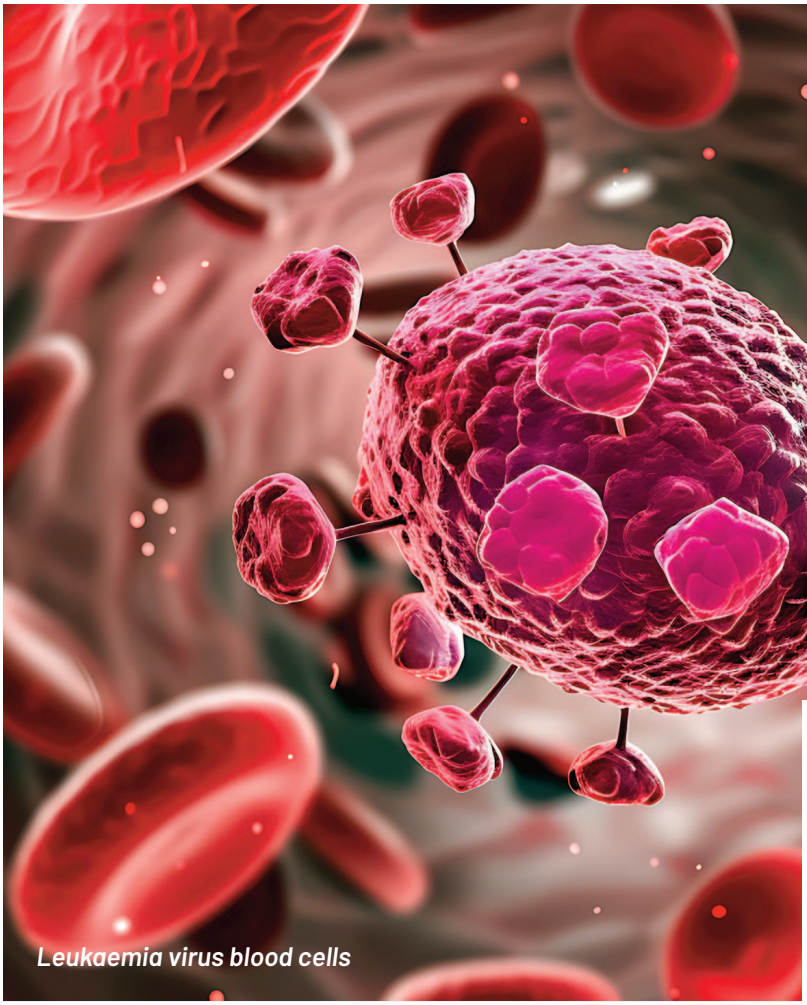
This analysis allowed the coordinator to formulate scientific conclusions regarding the patients' response to the pharmacological treatments used.

Table 1. PETHEMA (as per Oxford Index)

First Spanish medical society, non-commercial promoter of clinical studies in Medicine in European hospitals of the public health network.

Order	Sponsor	Number of studies
78	Fundació Clínic per a la Reçerca Biomèdica (Barcelona)	84 Clinical Trials
88	Vall d'Hebron University Hospital (Barcelona)	73 Clinical Trials
102	Hospital de la Santa Creu i Sant Pau (Barcelona)	67 Clinical Trials
143	PETHEMA Foundation (Madrid)	50 Clinical TrialsEU

Trials Tracker [Internet] [accessed 2025 Jun 2]. Available from: https://eu.trialstracker.net/?all



Leukaemia virus blood cells

Image: Freepik

established in parallel a real-time monitoring of their results, allowing them to agree on the continuous improvement of these same procedures.

With the continued development of research activity and the necessary legal and ethical regulation of clinical research, alongside major advancements in new drugs, clinical trials have become particularly important. In these, optimal experimental conditions are planned, and patients are selected and allocated according to rigid homogeneity criteria within a specific clinical study profile to test the efficacy and safety of new therapies. Clinical trials have been, and will continue to be, an indispensable tool for understanding the fundamental "behaviour" of new treatments in people, with a notable level of internal validity. However, in many cases, they are not sufficient to provide sufficient external validity to extrapolate their conclusions point by point to the entire population.[2]

It has therefore become necessary to go back to the origins and to recover a type of research that allowed us to obtain information from the real environment as a whole and from everyday healthcare practice with which to capture all the truthful information on the treatments used in all types of patients, i.e., RWD research. According to the agreed definition of RWD, this type of investigation includes all observational and registry studies, patient self-reported data (surveys, quality of life questionnaires, social media testimonials, among others), administrative databases, and electronic registry data (including laboratory data, digital medical records, and patient complaints, among others).[3,4]

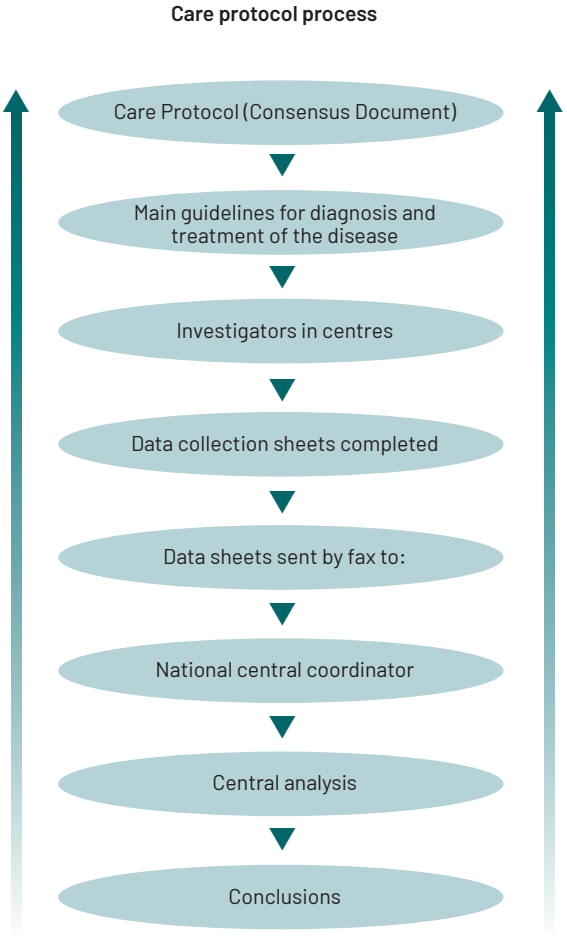


Figure 1. Key guidelines for disease diagnosis and treatment flowchart

Why is RWD crucial for personalised medicine in haematological malignancies?

RWD studies examine real-world conditions without discrimination or omission of patient type, collecting information from real clinical practice settings that are not pre-planned or pre-conditioned. They cannot replace the critical safety and efficacy data generated by clinical trials, but they can help to consolidate these data by allowing comparisons across a wide variety of real clinical settings.[2,5]

Thus, RWD research tends to provide more complete information on the safety and effectiveness of treatments in a wider variety of clinical settings.[5,6] They are therefore key to obtaining data on more hidden or subtle statistical trends that require large sample sizes (thousands or even hundreds of thousands), or much longer periods (several decades, even) to reveal.[7] This is especially necessary in haematological malignancies, where the constellation of biological variants makes it very difficult to obtain, in a clinical study setting, a sufficient sample of cases of a particular disease entity, such as a mutation or a specific set of them, for example. It is precisely in the study of haematological malignancies where a much greater abundance of information and cross-referencing of data is required due to the tremendous genetic and epigenetic phenomena that exist. On the other hand, RWD research is necessary in those types of research where it is not possible to set up more than a single arm, because they are serious and rare diseases where randomisation is often not feasible or ethically reprehensible, and where there is no choice but to rely on external control databases from clinical trials or previous RWD studies.[8]

Finally, RWD studies provide a type of information that can also be of great interest: patient-perceived outcomes.[9] This is particularly interesting in haematological malignancies, where the processes unfortunately often involve considerable morbidity.

Addressing the peculiarities of the main haematological malignancies – illnesses caused by the uncontrolled growth of bone marrow cells, which damage normal tissues and can lead to fatal bone marrow failure – we identified priority needs for RWD research, summarised as follows:

- **Monoclonal gammopathies (especially multiple myeloma):** These diseases are caused by the proliferation of a clone of mutated plasma cells (white blood cells responsible for antibody production) that secrete an abnormal protein (paraprotein). In multiple myeloma (MM), these cells grow without limits within the bones, leading to their destruction. In this field, RWD research is highly valuable for the complete and final evaluation of new therapies in patients with comorbidities who are often underrepresented in clinical trials. It also helps characterise predictive models of medium- and long-term response. This is of particular interest in smoldering myeloma (a relatively indolent hyperparaproteinemia that can sometimes progress to active myeloma) and in some specific genotypic profiles of MM.
- **Acute myeloblastic leukaemia (AML):** In this disease, the cellular proliferation originates from myeloid blood cells, and the critical damage, as in acute lymphoblastic leukaemia (ALL), is the eventual failure of the bone marrow. Here, RWD is crucial for a better understanding of prognostic values closely related to certain genetic mutations. Additionally, RWD can help define the optimal indication for hematopoietic stem cell transplantation for each case or clinical profile and for the exhaustive comparison of different treatments in very diverse patient populations.
- **Acute Lymphoblastic Leukaemia (ALL):** In this disease, the cellular proliferation originates from the lymphoid blood cells. RWD in this area is valuable for long follow-ups of patients with new targeted therapies and for comparing, across sufficient samples and different age strata, the various polychemotherapy regimens.
- **Bone marrow failure syndromes (BMFS):** The main disease in this group is aplastic anaemia, in which the bone marrow ceases to produce the daily quantity of cells necessary for the various functions of the blood. RWD is of interest here, above all, to obtain a sufficient database to study the response to immunosuppressive treatments and transplantation. This is especially important for disorders with such a low incidence, where gathering a sufficient sample to study any reality is always the greatest handicap.
- **Chronic myeloproliferative and lymphoproliferative processes:** These are less aggressive neoplastic proliferations of more mature cells from either myeloid or lymphoid lineages. RWD is of particular interest in assessing the impact of inhibitors in real-life settings, as well as in advancing the definition of more personalised treatments.
- **Lymphomas:** Cancer of the lymphatic nodes or spleen. RDW is highly valuable for long-term follow-up of patients treated with immunotherapy or emerging therapies in refractory conditions.

Across all these diseases, extensive biological research is crucial for discovering better, specific biomarkers to predict treatment response with greater precision.

Across all these diseases, extensive biological research is crucial for discovering better, specific biomarkers to predict treatment response with greater precision. This research also involves collecting more comprehensive information on idiosyncratic toxicities of new treatments or adverse reactions with delayed manifestations. In this latter aspect, RWD proves particularly useful for tracking second malignancies and for the complete study of certain more peculiar and unexpected toxicities. A good example of this is the novel CAR-T therapy, a modern, genetically-mediated immunological treatment that involves reprogramming the patient's lymphocytes by integrating new genetic information into their genome, enabling them to specifically recognise and attack malignant cells.

PETHEMA's experience so far at RWD

PETHEMA is active on several research fronts where RWD research is providing a decisive push towards a better understanding of diseases and their treatments. This work is carried out by the main study groups that make up PETHEMA, principally the Spanish Myeloma Group (GEM), the AML group and the ALL group. PETHEMA's experience to date in this area focuses mainly on AML, ALL, and MM, but includes interesting work in other areas like bone marrow failure.

PETHEMA's AML group holds a unique asset, allowing extensive RWD research and diverse analytical approaches. This refers to the AML epidemiological registry, which has stored all clinical data and much of the correlated biological data from over 24,600 patients diagnosed with AML, including about 5,300 with the acute promyelocytic leukaemia (APL) subtype, for several decades. Drawing on this vast

Close-up -blood cells – leukocytes erythrocytes bloodstream

Image: Freepik

number of cases (mostly thousands) of certain predefined clinical profiles, valuable published research has been conducted. These studies have described special patient populations,[11-16] and they've validated certain pharmacological treatments,[14,17,18,] even demonstrating advantages over others.[12,19,20-27] This research has also shown the suitability of allogeneic transplantation for AML treatment and analysed the incidence of secondary malignancies.[12,15,19,20-24,27] Furthermore, it's allowed for comparisons with historical external controls,[21,28,29] and importantly, it's demonstrated the prognostic value of Minimal Residual Disease (MRD) and its key role in risk stratification.[30,31] Above all, a huge amount of molecular data has been studied to better characterise clinical and genetic patterns linked to treatment responses and their associated prognoses.[13,14,15,18,22-26,28,29,31-34]

Research conducted within PETHEMA's Spanish Myeloma Group (or Grupo Español de Mieloma; GEM) is tremendously prolific through clinical trials. RWD research is less abundant but equally interesting, and has been carried out mainly through various observational and translational studies. At this point, we highlight studies carried out for the evaluation of certain special patient populations,[35] studies to verify the validity of certain pharmacological treatments or their superiority compared to others,[36,37] the characterisation of genetic profiles associated with different prognostic value[38,39] or other studies due to imminent or future publication that confirm the validity of monitoring MRD in MM for the optimisation of disease management (EMR-Clinical study, pending to be promptly published) or that search for factors predictive of transformation to MM, amyloidosis, Waldeström macroglobulinemia, or of complication to a severe infection (NoMoreMGUS).

In the area of ALL, the main RWD work is based on observational studies that have demonstrated the prognostic value of MRD in Phi-negative ALL patients, compared different treatment regimens, and measured the impact of allogeneic transplantation versus chemotherapy alone.[40,41] On the other hand, the ALL Group decided to collaborate with the Harmony Alliance in order to establish conclusions of prognostic value for a certain type of mutation,[43,44] or to analyse a huge amount of biological data to define genetic patterns associated with specific treatment responses and differing prognoses. The HARMONY Alliance is the European academic entity responsible for an initiative that collects extensive big data from several haematological malignancies. This data is obtained from numerous clinical trials and observational studies conducted by many European research groups. It is worth noting that several papers have already been published from this collaboration, with some involving the PETHEMA group.

In the field of bone marrow failure, an observational study published last year paradoxically revealed worse survival outcomes in patients with a moderate bone marrow aplasia profile compared to those with a severe or very severe profile.[45] There are also two soon-to-be-published ongoing observational studies (PIRE and APPRI-PNH), which will analyse the therapeutic outcomes of patients with paroxysmal nocturnal haemoglobinuria (PNH) treated with a different complement inhibitor in each study.

Problems of research with RWD

Extensive literature debates whether RWD research truly meets full quality standards, given that it may bypass certain rigours of Cartesian research developed through clinical trials.[46] What is certain, however, is that as with all research, its ultimate validity rests with the researchers. These individuals, aware of RWD's limitations and

adhering to necessary precautions, can achieve truly reliable results.[47]

Managing a huge amount of information is a key limitation of RWD research. The sheer scale and diversity of this data require powerful and complex computer equipment, which presents a substantial problem due to the high costs of both using and maintaining the necessary infrastructure.[48] These costs are mainly related to the need for continuous review and updating of data and data quality, modifications to the source system, changes in system specifications, and identifying variations in implementation between sites to address the challenges of incompatibilities that arise between different information and analysis systems. Another limitation is the fact that some differences between data from different sites cannot be resolved by a standardised data model and require a close level of cooperation with site staff to overcome difficulties in unambiguously interpreting information. Confounding factors are a significant challenge when comparing the effectiveness and safety of treatments using real-world data, particularly due to the data's diverse nature. Rigorous control of design and analytical fit is required to obtain consistent and truthful estimates that withstand any test of irrefutability.[49]

Regarding ethical issues, the growing problem of strict, regulated, explicit informed consent in RWD research warrants attention, particularly where the routine use of data must be intensive and fluid.[50] Similarly, rigorous data pseudo-anonymisation policies, while attempting to protect privacy at all costs, sometimes exceed what is reasonable. This hinders the rapid and efficient obtaining of sufficient quality information in complicated clinical or highly relevant public health issues.[51]

Reflections on the future

The refinement of clinical research and the trend towards maximum sample universalisation (aiming not to lose a single study-worthy case) will exponentially increase the complexity of work systems. These systems will, in turn, become increasingly dependent on technological advances. The use of artificial intelligence is already a fact and will continue to gain ground here, as in many other areas of scientific activity. This aligns with the need to acquire the enormous capacity to analyse highly specific and often hidden biological data, detecting their logical clinical and biological interrelationships. This will allow conclusions to be drawn that are impossible with conventional statistical analyses.

The widespread use of nano-robotics, which is already being explored for certain therapeutic purposes, may also have an exciting role to play in the precise and immediate collection of intracorporeal intimate cellular and biological niche data.

Progress in improving clinical (patient-centred) and biological (lab work) diagnostic tools and techniques is essential. We need to make them more reliable, faster, more efficient, and less invasive, not only to advance research but also to improve medical practice. Additionally, further work is needed to improve patient compliance with wearable devices by making them more discreet, efficient, and less disruptive to daily life.

Finally, in the defence of scientific freedom, we must offer a constructive critique of regulatory issues. This critique is presented as the authors' personal opinion, with the sole aim of stimulating healthy reflection on how to improve scientific progress. Certain issues in this respect should provoke a paradigm shift in the legislator's approach to facilitate the transition towards a more scientifically productive future that is ultimately pragmatically useful to humanity.

Data protection legislation seeks to protect fundamental rights, but it can significantly impede the dynamism in the exercise of scientific freedom. This freedom, it is crucial to remember, always seeks the greater common good of scientific progress and the advancement of human well-being. A new balance in this game of defence between individual and collective rights needs to be fostered in this area. This would allow the global medical-scientific research system to function better without compromising fundamental protections.[52] Science consistently outpaces the law, so there is an imperative need for regulators and legislators involved in the control of health research activity to urgently adapt to the needs of scientific discovery. They need to shape new principles to harmonise the most appropriate approach to operational efficiency, ethics, and governance globally.[52,53]

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Disclaimers

The opinions expressed in this article are the authors' own and not necessarily shared by their employer, the PETHEMA members, or EMWA.

Disclosures and conflicts of interest

The authors declare no conflicts of interest.

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