Deliverable 7.1

Report on state of the art of Clinical Trials in Rare Hematological Diseases

European Reference Network
for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

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Short description: Report on on-going clinical trials for rare hereditary anemias and actions to promote clinical research in the context of ERN-EuroBloodNet

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1- Clinical research on rare hereditary anemias: challenges

While individually rare, rare diseases (RDs) collectively are actually quite common, with an estimated 350 million sufferers worldwide. From this, between 27 and 36 million people are estimated to be living with a RD in the European Union (EU).

A RD is defined according to the European legislation as a condition presenting a prevalence threshold of not more than five affected persons per 10,000 individuals (Regulation (EC) N°141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products). There exist between 6,000 and 8,000 RDs. RDs research poses challenges to investigators requiring among others specific approaches to: a) the design of clinical studies; b) the funding of research programs; and c) the discovery, testing, and approval of new treatments.

The so-called "orphan drugs (OD)" are intended to treat RDs, which due to their rarity, are not are attractive to sponsors, who are reluctant to develop them under the conditions market, since the small size of the market to which they are aimed would not allow recover the capital invested in the research and in the development of the product. Since the introduction of the Orphan Drug Act in the US more than 30 years ago, followed by legislation in Japan in the 1990s, and the EU Regulation on Orphan Medicinal Products in 2000, the number of orphan designations has skyrocketed. There are currently around 566 ODs in development, encompassing many different therapeutic areas.

The European Medicines Agency (EMA) plays a central role in facilitating the development and authorisation of ODs. OD according to the European Union is: That product intended for an indication whose prevalence does not exceed 5 cases per 10,000 inhabitants in the European Union (EU). Being also a life-threatening disease, it is very debilitating or is a serious and chronic condition. Disease for which there is no satisfactory method of diagnosis, prevention or authorized treatment in the EU. If there is a method, then the drug must show that it provides a significant benefit compared to the product already authorized.

The designation of orphan drug is requested voluntarily and free of cost because with it can benefit from the incentives provided for in the regulation, without which the marketing of said medicine would not generate enough income to justify the investment necessary. The designation in no way establishes that the medication is safe or effective and neither It allows us to know the research phase in which the product is located, but if it indicates that the medicine meets the definition of an orphan established by the European Commission.

However, despite the strong financial and regulatory incentives introduced by the legislation, drug development programmes for the treatment of RDs still face many challenges. These include the small number of patients available, poor understanding of the disease, difficulties associated with trial design, and challenges with patient enrolment and retention.

The scenario is not different for rare hereditary anaemias (RHAs). RHA embraces a highly heterogeneous group of disorders, including rare and ultra-rare haematological conditions. RHAs were prioritized for an action in the frame of ERN-EuroBloodNet since they encompasses, with few exceptions as hemoglobinopathies, many ultra-rare conditions related to red blood cell disorders, bone marrow failures and iron metabolism disorders which are not currently well covered due to their scarce expertise, lack of appropriate funding and policies and low patients involvement.

RHAs are characterized by anaemia of variable degree, from mild forms to life threatening chronic blood-transfusion dependence, and by complex and often unexplained genotype-phenotype correlations. RA are genetic disorders caused by mutations in more than 70 genes controlling red blood cell (RBC) production and structure. These mutations lead to alterations in haemoglobin (Hb) levels, RBC differentiation, proliferation and survival, cell membrane structure, and defective activity of erythrocyte enzymes. The balance between haemolysis, mainly in the spleen, and (ineffective) erythropoiesis partly explains the severity of RA patients and their capability to respond to treatments. Common symptomatic treatments for RA include regular RBC transfusions and splenectomy. Nevertheless, both are considered as risk factors for iron overload. Recent advances in the molecular basis underlying RHAs has led to a number of new drugs currently in clinical trials as well as gene therapy approaches, however few drugs are yet on the market.

2-Objectives

ERN-EuroBloodNet established five specific objectives as priorities to be accomplished in the frame of the 5 years of implementation, including the specific objective 5: Foster European cooperation in highly specialized procedures for diagnosis, innovative treatments and research

This objective aims to contribute to the EHA roadmap for European Hematology Research by supporting the creation of a European patient registry in RHD, promoting the access to clinical trials, facilitating the provision of –omics platforms and new technologies and fostering research projects in druggable targets identification, gene therapy and pathophysiology.

In line with the specific objective 5, **the present deliverable aims to describe the methodology defined for the promotion of clinical research on rare hereditary anemias in the frame of ERN-EuroBloodNet.**

3-Activities implemented

3.1. Desk research on clinicaltrials.gov

In order to establish the state of the art of on-going clinical trials for rare hereditary anaemias (RHAs) a desk research was conducted on ClinicalTrials.gov website.

ClinicalTrials.gov is a database of privately and publicly funded clinical studies conducted around the world. It is a resource provided by the U.S. National Library of Medicine.

Sponsors or investigators of certain clinical trials are required by U.S. law to register their trials on and submit summary results to ClinicalTrials.gov. Other international policies also require trial registration.

Each study record includes a summary of the study protocol, including the purpose, recruitment status, and eligibility criteria. Study locations and specific contact information are listed to assist with enrollment.

Some study records include summary study results in a tabular format. The results information submitted to ClinicalTrials.gov includes the number of participants starting and completing the study, baseline characteristics, outcome measures, and adverse events.

122 "Search terms" covering 105 disorders classified as rare hereditary anemias were established based on ORPHA classification. For each one, the following parameters were included in the search:

a) Study type: Describes the nature of a clinical study. Study types include:

- Interventional studies (also called clinical trials)
- Observational studies (including patient registries)
- Expanded access.

b) Status regarding recruitment:

- Not yet recruiting: The study has not started recruiting participants.
- Recruiting: The study is currently recruiting participants.
- Enrolling by invitation: The study is selecting its participants from a population, or group of people, decided on by the researchers in advance. These studies are not open to everyone who meets the eligibility criteria but only to people in that particular population, who are specifically invited to participate.

- Active, not recruiting: The study is ongoing, and participants are receiving an intervention or being examined, but potential participants are not currently being recruited or enrolled.

For the avoidance of doubt, the following status regarding recruitment were not included:

- Suspended: The study has stopped early but may start again.
- Terminated: The study has stopped early and will not start again. Participants are no longer being examined or treated.
- Completed: The study has ended normally, and participants are no longer being examined or treated (that is, the last participant's last visit has occurred).
- Withdrawn: The study stopped early, before enrolling its first participant.
- Unknown: A study on ClinicalTrials.gov whose last known status was recruiting; not yet recruiting; or active, not recruiting but that has passed its completion date, and the status has not been last verified within the past 2 years.

c) Status regarding expanded access:

- Available: Expanded access is currently available for this investigational treatment, and patients who are not participants in the clinical study may be able to gain access to the drug, biologic, or medical device being studied.
- Temporarily not available: Expanded access is not currently available for this intervention but is expected to be available in the future.
- Approved for marketing: The intervention has been approved by the U.S. Food and Drug Administration for use by the public.

For the avoidance of doubt, the following status regarding recruitment was not included:

- No longer available: Expanded access was available for this intervention previously but is not currently available and will not be available in the future.

d) Age group: A type of eligibility criteria that indicates the age a person must be to participate in a clinical study. This may be indicated by a specific age or the following age groups:

- Child (birth-17)
- Adult (18-64)
- Older Adult (65+)

e) Phase: The stage of a clinical trial studying a drug or biological product, based on definitions developed by the U.S. Food and Drug Administration (FDA). The phase is based on the study's objective, the number of participants, and other characteristics. There are five phases:

- Early Phase 1 (formerly listed as Phase 0)
- Phase 1
- Phase 2
- Phase 3
- Phase 4
- Not Applicable is used to describe trials without FDA-defined phases, including trials of devices or behavioral interventions.

Results for each search term were download in comma-separated values including All Available Columns. This includes over 20 columns such as Status, Conditions, Interventions, Study Type, Phase, and Sponsor/Collaborators. Comma-separated values format save each study as a separate line in the file, with commas as delimiters, or spacers, between each field. This format is useful for importing study information into spreadsheets and databases.

Information obtained was analyzed to establish the number of on-going clinical trials focused on each condition, type of interventions, geographical coverage and ERN-EuroBloodNet members involvement. Duplications were removed and disease focus was checked for consistency.

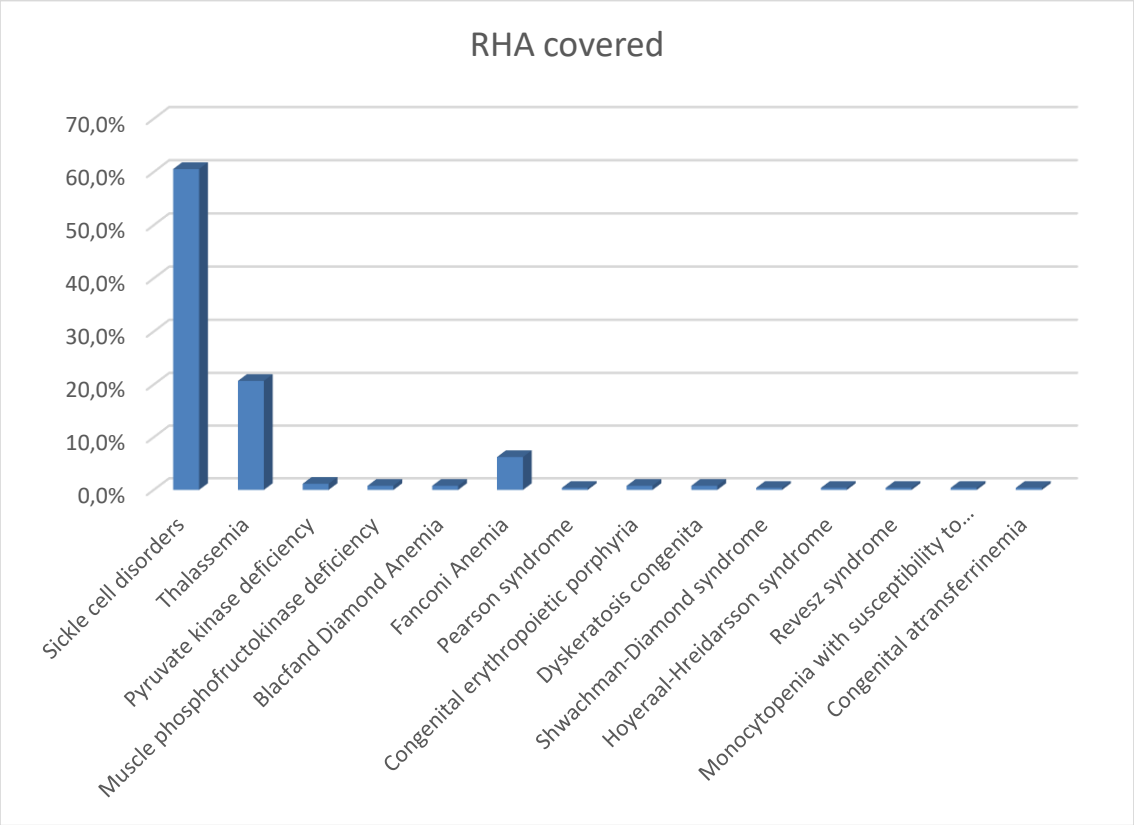
4- Results

From the 122 Search terms, only 28 of them get some result from the search, covering 26 RHAs from the : Sickle cell disorders (6 types), beta- Thalassaemia (7 types), Hemoglobin H disease (2 types), Pyruvate kinase deficiency, Muscle phosphofructokinase deficiency, Congenital erythropoietic porphyria, Blackfan-Diamond anemia, Dyskeratosis congénita, Fanconi anemia, Revesz síndrome, Hoyeraal-Hreidarsson syndrome, Shwachman-Diamond syndrome, Monocytopenia with susceptibility to infections and Congenital atransferrinemia. A total of 256 CTs resulted from the analysis after removing duplications and assess quality of data regarding disease focus. 24 of them not focused on a concrete disorder but on a large group of hematological disorders. Number od CTs by concrete disorders are shown in Table 1 and Figure 1. Regarding interventions, 103 involve drug, 72 involve bone marrow transplant, 21 involve gene therapy and 60 involve other type of interventions as devices, behavior…etc. See Table 1.

Table 1 – List of CTs and breakdown according to disease and intervention

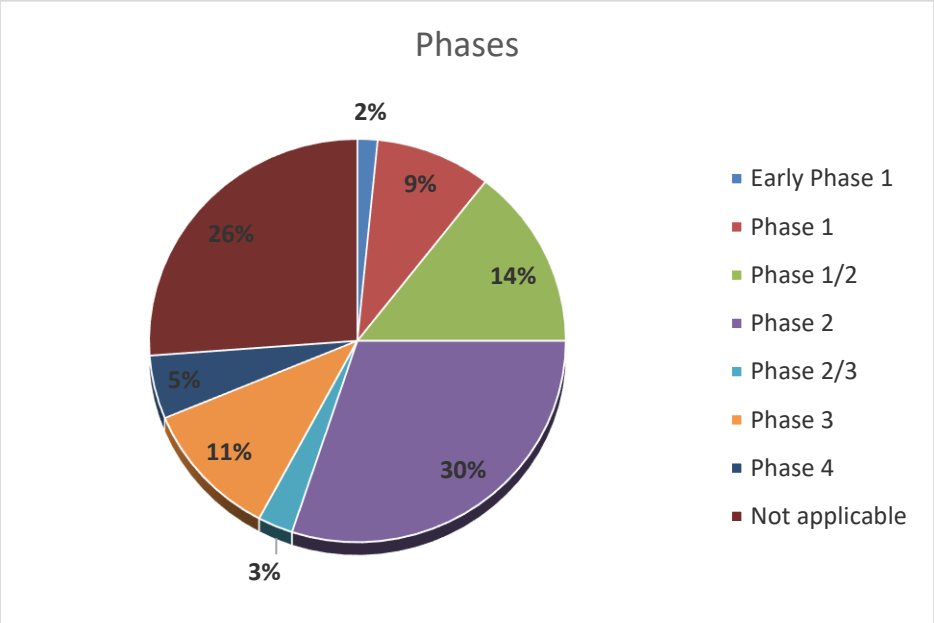
CTs "Rare Hereditary Anemias" Search terms	**256**	
Without focus on a concrete condition	**24**	**9.4%**
Rare hematological disorders (RHD)	10	3,9%
Oncological RHD	3	1,2%
non-Oncological RHD	10	3,9%
Hemolytic anemia	1	0,4%
With focus on (a) concrete condition (s)	**232**	**90.6%**
Sickle cell disorders	155	60,5%
Thalassemia	53	20,7%
Pyruvate kinase deficiency	3	1,2%
Muscle phosphofructokinase deficiency	2	0,8%
Blacfand Diamond Anemia	2	0,8%
Fanconi Anemia	16	6,3%
Pearson syndrome	1	0,4%
Congenital erythropoietic porphyria	2	0,8%
Dyskeratosis congenita	2	0,8%
Shwachman-Diamond syndrome	1	0,4%
Hoyeraal-Hreidarsson syndrome	1	0,4%
Revesz syndrome	1	0,4%
Monocytopenia with susceptibility to infections	1	0,4%
Congenital atransferrinemia	1	0,4%
Drugs	**103**	**40,2%**
Bone marrow transplant	**72**	**28,1%**
Gene Therapy	**21**	**8,2%**
Other	**60**	**23,4%**

Figure 1 – CTs in % by RHA



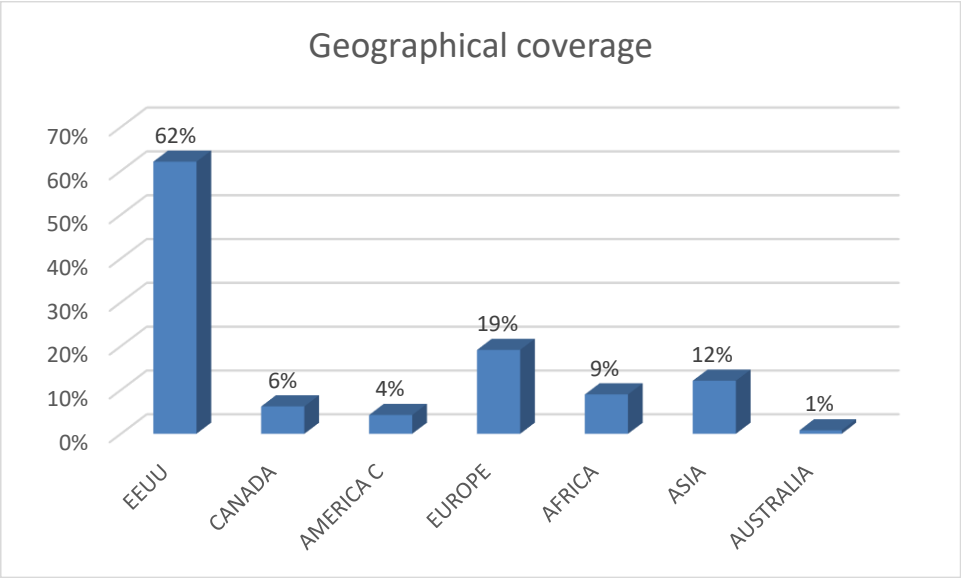
Regarding Phases, 4 CTs were listed for Early Phase 1, 23 for Phase 1, 37 for Phase 1/2, 77 for Phase 2, 7 for Phase 2/3, 28 for Phase 3, 13 for Phase 4, and in 67 Phase was not applicable. See figure 2.

Figure 2 – CTs breakdown in Phases (%)



Regarding geographical coverage, 43 of the 256 CTs are International (17%), meanwhile 213 are only open in a single country (83%). Concretely, 159 CTs are open in EEUU, 16 CTs in Canada, 11 CTs in America – Central, 49 CTs in Europe, 23 CTs in Africa, 31 CTs in Asia and 2 in Australia. See figure 3.

Figure 3 – Geographical coverage of CTs for RHA



When coming to specific disorders concentrating the majority of CTs; sickle cell disorders, thalassaemia and Fanconi Anemia, results are the following:

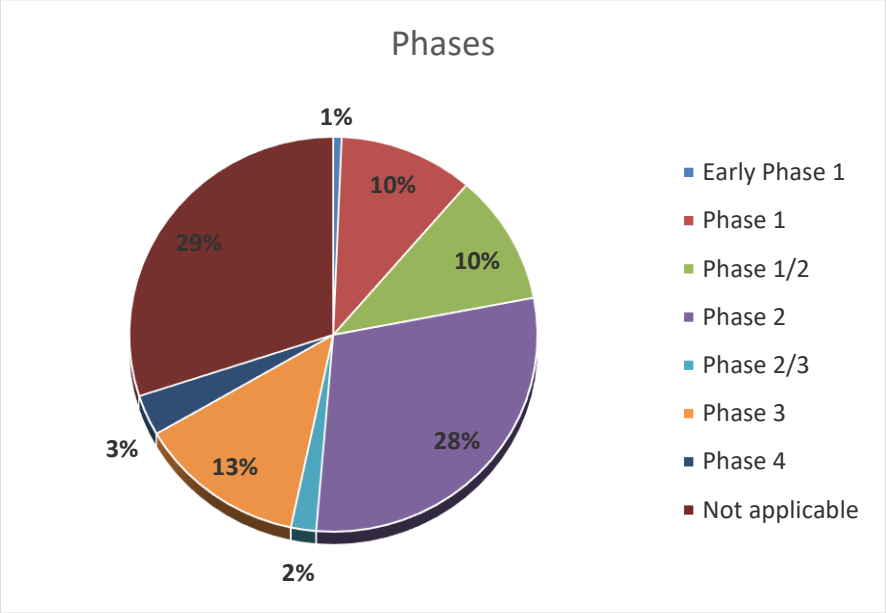
For Sickle cell disorders, there are 169 on-going CTs, 155 of them focused on the disease. Regarding interventions, 67 involve drug, 33 involve bone marrow transplant, 7 involve gene therapy and 44 involve other type of interventions as devices, behavior…etc. See Table 2.

Table 2 – SCD CTs and breakdown according to intervention type

CTs Search term "Sickle cell disorder"	169	
CTs focussed on "Sickle cell disorder"	155	91,72%
Drugs	67	43,23%
Bone Marrow Transplant	33	21,29%
Gene Therapy	7	4,52%
Vaccination	3	1,94%
Transfusion	1	0,65%
Other	44	28,39%

Regarding Phases, 1 CTs were listed for Early Phase 1, 16 for Phase 1, 16 for Phase 1/2, 44 for Phase 2, 3 for Phase 2/3, 20 for Phase 3, 5 for Phase 4, and in 45 Phase was not applicable. See figure 4.

Figure 4 – SCD CTs breakdown in Phases (%)



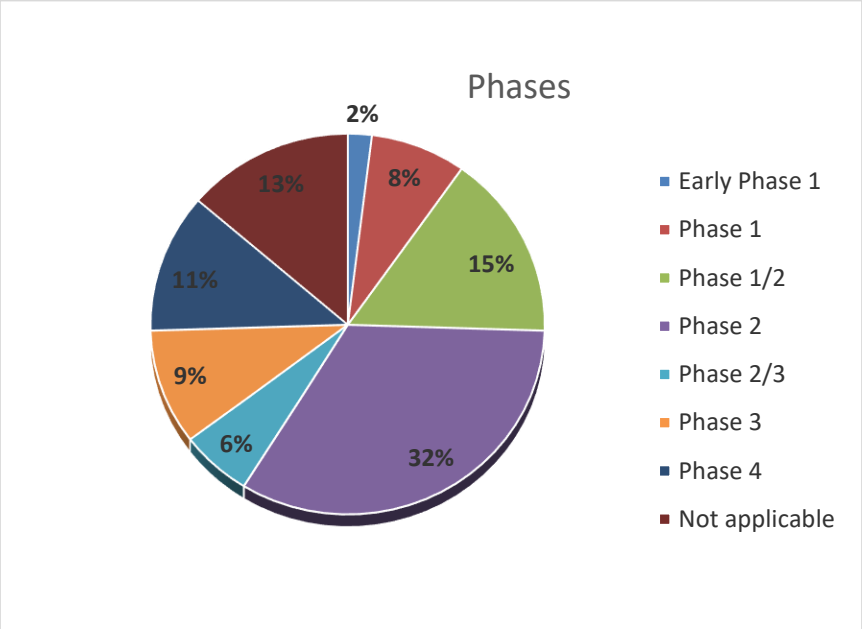
For Thalassaemia, there are 75 on-going CTs, 53 of them focused on the disease. Regarding interventions, 26 involve drug, 13 involve bone marrow transplant, 10 involve gene therapy and 4 involve other type of interventions as devices, behavior…etc. See Table 3.

Table 3 – Thalassaemia CTs and breakdown according to intervention type

CTs Search term "Thalassaemia"	75	
CTs focussed on "Thalassaemia"	53	70,67%
Drugs	26	49,06%
Bone Marrow Transplant	13	24,53%
Gene Therapy	10	18,87%
Other	4	7,55%

Regarding Phases, 1 CTs were listed for Early Phase 1, 4 for Phase 1, 8 for Phase 1/2, 17 for Phase 2, 3 for Phase 2/3, 5 for Phase 3, 6 for Phase 4, and in 7 Phase was not applicable. See figure 5.

Figure 5 – Thalassaemia CTs breakdown in Phases (%)



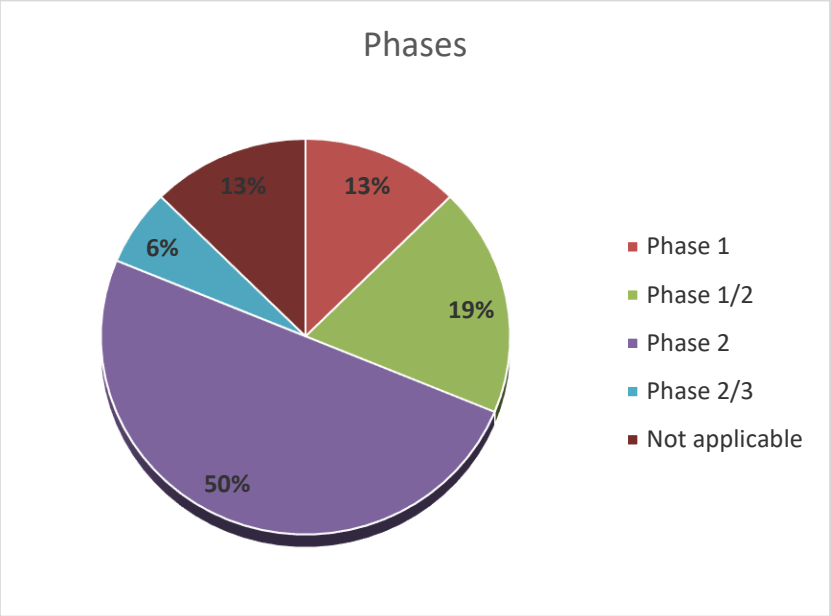
For Fanconi anemia, there are 16 on-going CTs, all of them focused on the disease. Regarding interventions, 2 involve drug, 8 involve bone marrow transplant, 4 involve gene therapy and 2 involve other type of interventions as devices, behavior…etc. See Table 4.

Table 4 – Fanconi anemia CTs and breakdown according to intervention type

CTs Search term "Fanconi anemia"	16	
CTs focussed on "Fanconi anemia"	16	100,0%
Drugs	2	12,5%
Bone Marrow Transplant	8	50,0%
Gene Therapy	4	25,0%
Drugs	2	12,5%
Other	2	12,5%

Regarding Phases, 2 for Phase 1, 3 for Phase 1/2, 8 for Phase 2 and 1 for Phase 2/3. See figure 6.

Figure 6 – CTs breakdown in Phases (%)



5- ERN - EuroBloodNet projects on clinical trials in rare hereditary anemias

Only 26 RHA from the 105 disorders classified as RHA (25%) are currently covered by at least one CT. This means that for 3 out of 4 very rare RHA no CT is available, thus no new therapeutic option. RHA not covered by any CTs include in particular a) chronic hemolytic anemias due to membrane disorders or channelopathies, as Hereditary Spherocytosis, Hereditary Ellyptocytosis, and Overhydrated / Dehydrated hereditary stomatocytosis, b) constitutional dyserythropoietic anemias and most c) hemolytic anemias due to a enzymatic deficiency, d) constitutional sideroblastic anemias and e) constitutional anemia due to iron metabolism disorder. In addition, only 19% of the CTs are open in Europe and from this, only around the 50% are active in ERN-EuroBloodNet members from only 5 member states.

Those results demonstrate urgent need to improve the access to CTs of patients affected by RHA across EU. ERN-EuroBloodNet has therefore started to initiate clinical trials in this field, and is planning other actions:

1) We have started to conduct academic CTs in very rare diseases in which pharmaceutical companies have not planned CT. This includes Ie.

a) *Luspatercept* (an inhibitor of the transforming growth factor beta (TGF-β) superfamily) in Congenital Dyserythropoietic Anemia type II (CDAII) and congenital sideroblastic anemias, diseases requiring require regular red blood cell transfusions. Luspatercept, in those disorders, should be able to induce differentiation of erythroid cells, improve ineffective erythropoiesis, correct anemia and limit iron overload. Trial principal investigators will be A Iolascon (Italy) and O Hermine (France), both centers being active HCP in EuroBloodNet

b) *Senicapoc* in dehydrated hereditary stomatocytosis (DHS), also known as hereditary xerocytosis, a ultra-rare hemolytic anemia characterized by a decreased red cell osmotic fragility due to a defect in cation permeability, resulting in red cell dehydration and compensated hemolysis of different degrees. No treatment is available for this condition. Senicapoc (also known as ICA-17043) is a potent blocker of the Gardos channel, a calcium-activated potassium channel of intermediate conductance, in the red blood cell. Preclinical studies and studies in transgenic models of SCD show that inhibition of potassium efflux through the Gardos channel

is associated with an increased hemoglobin level, decreased dense cells and decreased hemolysis. (principal investigator L Garçon).

To conduct those trials, EuroBloodNet has recruited a clinical research team to carry out trial promotion and data monitoring. The main sponsor for each trial will be the university hospital of the principal investigator. Participation of other EU countries will be possible by defining delegate sponsors in those countries (generally university hospitals), according to the EU directive on clinical trials. We will also cooperate closely with companies for drug storing and shipping, and for pharmacovigilance

2) We are Identifying CTs using highly innovative treatments whose availability is limited in some EU-MS due to budget restrictions, lack of diagnostic procedures or various infrastructures, etc… Our purpose would be contribute to set up conditions for implementation of such CTs in those EU members and or specific centers.

3) We are also identifying HCPs which are currently not ERN-EuroBloodNet members but are very active in CTs for RHA in order to invite them to join the ERN in the upcoming Call for new membership.