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Defining the natural history of rare genetic liver diseases: Lessons learned from the NAPPED initiative

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ABSTRACT

While rare diseases collectively affect ~300 million people worldwide, the prevalence of each disease concerns a relatively small number of patients. Usually, only limited data with regard to natural history are available. Multicenter initiatives are needed to aggregate data and answer clinically relevant research questions. In 2017, we launched the *Natural course and Prognosis of PFIC and Effect of biliary Diversion* (NAPPED) consortium. In three years, NAPPED created a global network focused on rare genetic liver diseases in the Progressive Familial Intrahepatic Cholestasis (PFIC) spectrum. During these years, we have learned important lessons which we feel should be taken into account when initiating and leading a global consortium.

First, it is essential to 'keep it simple' from the start. Research questions, case report forms (CRFs) and data acquisition should be limited and clear to stay focused and keep the workload low for new participants. Secondly, early rewards and research output are needed to keep momentum and motivation. Quick output can only follow a clean and simple design. Thirdly, the leading team should be in touch and accessible. Ideally, an involved PhD-candidate is appointed as primary contact person. Lastly, be inclusive and actively involve all participants the consortium's course.

Global consortia are critical for personalized medicine in rare diseases. Also, they are essential for setting up trials to investigate generic drugs and personalized therapies. We hope to herewith stimulate others that are starting (or are planning to start) a global consortium, ultimately to help improve the care for patients with a rare disease.

1. Introduction

Per definition of the European Union (EU), a disease is considered rare if its prevalence is not more than 50 per 100,000 individuals ([The European Parliament and the Council of the European Union, 2000](#)). It is estimated that 80% of the roughly 8000 rare diseases identified so far

are genetic diseases. Collectively, rare diseases affect ~4% of the global population, totaling to ~300 million people worldwide ([Nguengang Wakap et al., 2020](#)). The prevalence of each rare disease itself concerns only a relatively small number of patients, which may or may not be geographically clustered. As a consequence, only limited information with regard to the natural history is available for most of these diseases.

Abbreviations: ABCB11, (ATP-binding cassette, sub-family B member 11); ATP8B1, (Phospholipid-transporting ATPase IC); BSEP, (Bile Salt Export Pump); CRF, (Case Report Form); EU, (European Union); FIC1, (Familial Intrahepatic Cholestasis Protein Type 1); NAPPED, (NATural course and Prognosis of PFIC and Effect of biliary Diversion); PFIC, (Progressive Familial Intrahepatic Cholestasis); PIP, (Pediatric Investigation Plan).

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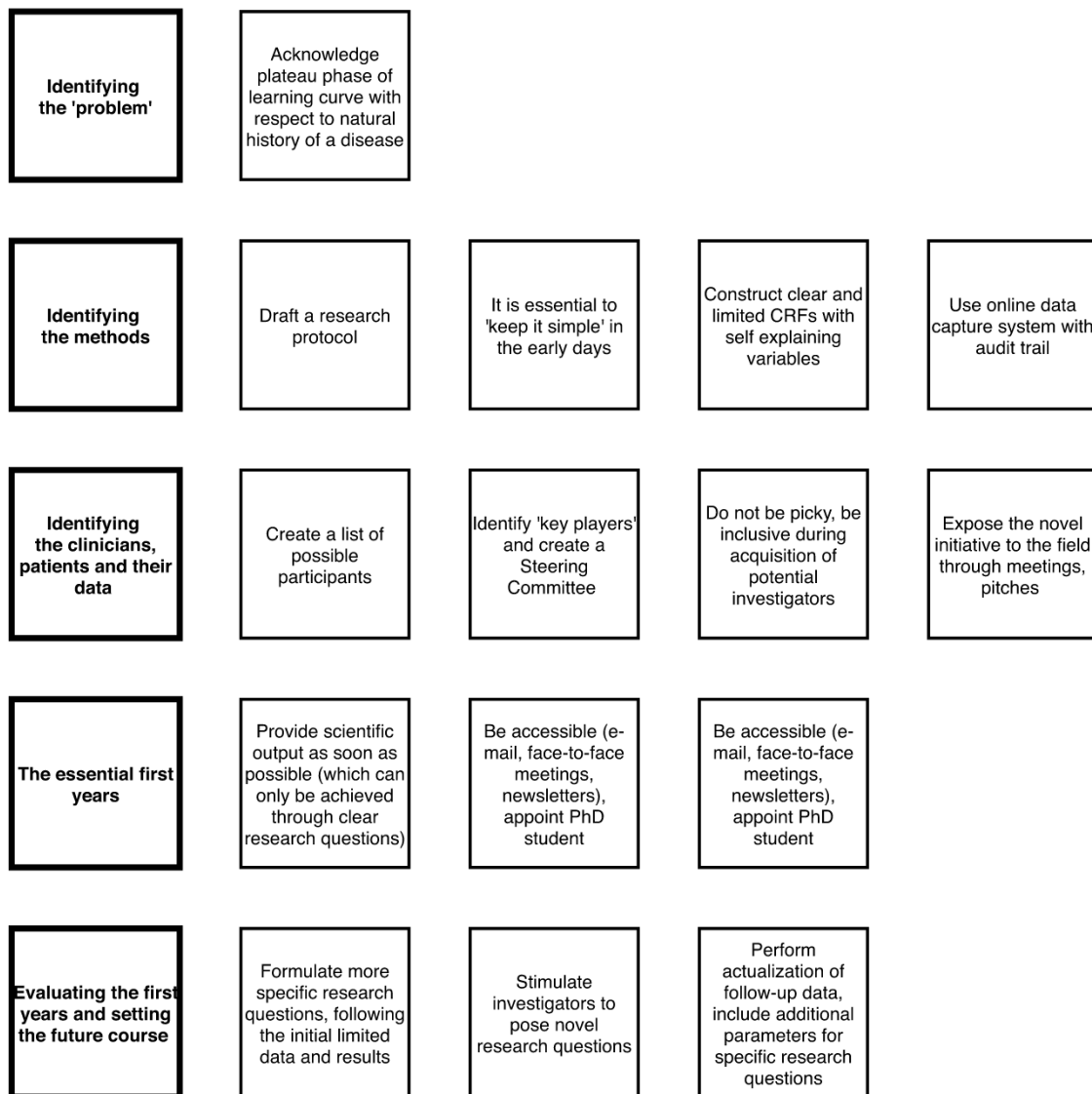


Fig. 1. Overview of key points per development phase.

It has therefore increasingly been recognized that international, multi-center initiatives are needed, in order to aggregate patient data and answer clinically relevant research questions, for example in terms of natural history, genotype-phenotype associations and responsiveness to surgical and medical treatments (US FoodAdministration, 2019). In the area of hepatology, a multitude of rare liver diseases exists, among which are various types of hepatocellular genetic cholestasis including Progressive Familial Intrahepatic Cholestasis (PFIC).

1.1. The NATural course and prognosis of PFIC and effect of biliary diversion' consortium

In 2017, we launched the NATural course and Prognosis of PFIC and Effect of biliary Diversion (NAPPED) initiative (van Wessel et al., 2018, 2021). Our aim was to increase the insights into the natural history, genotype-phenotype associations and the associations between treatments and long-term outcome in patients with either of two types of PFIC; severe deficiency of the Familial Intrahepatic Cholestasis Protein type 1 (FIC1), encoded by *ATP8B1*, also known as Progressive Familial Intrahepatic Cholestasis type 1 (PFIC1) or severe deficiency of the Bile Salt Export Pump (BSEP), encoded by *ABCB11*, also known as PFIC2 (Strautnieks et al., 1998; Bull et al., 1998). FIC1 and BSEP are

canalicular proteins involved in bile formation by contributing to the canalicular membrane bilayer asymmetry and by transporting bile acids, respectively. Patients affected by these diseases present a phenotype of progressive cholestasis, normal/low serum gamma-glutamyl transferase activity level, elevated serum bile acids, severe pruritus and in case of the PFIC1 spectrum, extrahepatic manifestations such as diarrhea and pancreatitis (van Wessel et al., 2020, 2021; Davit-Spraul et al., 2010). A surgical biliary diversion may be of benefit in some patients. This invasive procedure aims to bypass the terminal ileum (where 95% of excreted bile acids are reabsorbed and transported back toward the liver), by diverting bile from the gallbladder outside the body through a jejunostomy. The success rate ranges from full relief of symptoms to no benefit at all. Currently, no EMA approved drug is available for these diseases. The motivation for our consortium was primarily academic and patient-centered: we considered it quite likely that better insights into the variations in the phenotype and natural history would help to improve and personalize the care of the patients. Moreover, it could benefit the counseling and care of individual patients by health care professionals, which by themselves would only have a limited experience with the disease. The initiative was spurred by regulatory developments with respect to evaluation of the efficacy of novel experimental products, for example by the introduction of pediatric

investigation plans (PIP). Since the ‘European Union Pediatric Regulation’ came into force in January 2007 (The European Parliament and The Council of the European Union, 2006), all applications for European market authorization require a PIP. A PIP ensures that necessary data are obtained through studies in children. To address the consequences for pharmaceutical companies, it was decided that completed PIPs upon regulatory approval offer as reward a six-month extension of patent protection in case of non-orphan drugs. In case of orphan drugs, companies are rewarded a two-year extension of market exclusivity.

Finally, preclinical studies could lead to candidate pharmaceutical interventions that at some point would need to be evaluated in patients. Understanding the natural history of a disease would then be essential to determine if, and to what extent, a novel treatment or intervention has long-term beneficial effects. The rarity of the diseases limits the full-scale application of sufficiently powered, randomized placebo-controlled study designs.

At present, we have accumulated the largest genetically defined cohort of patients with severe FIC1 and BSEP deficiency known to date (>800 patients included). Our data allow tailoring medical and surgical therapies to the level of individual patients, based on the specific mutations causing these rare diseases. For example, we identified patients that do and patients that do not benefit from biliary diversion surgery, as well as those that are at high risk (up to 34%) of developing hepatocellular carcinoma in childhood (van Wessel et al., 2020). The natural cohort allows to search for surrogate endpoints and supports sample size calculations for design of new studies. Over the last three years, we have been learning important lessons, which we feel may be of benefit to the scientific community and may stimulate similar initiatives for other rare (liver) diseases. In the following paragraphs, we give a chronologic overview of important phases during the development of our consortium and of relevant issues we feel should be taken into account when initiating and leading a global study group. Fig. 1 provides an overview of these phases.

1.2. Identifying and acknowledging the ‘problem’

One of the major ‘problems’ in the study of rare diseases regards the low sample sizes that individual health care professionals inevitably encounter. Although small study cohorts and study designs which result from the low number of patients have undisputedly led to scientific breakthroughs, the low number of patients usually does not allow to thoroughly address the natural history of a disease, genotype-phenotype associations and efficacy and (non-)eligibility for surgical or medical treatment strategies. A common chronology in the study of a rare disease starts with the initial description of a syndrome (potentially initiated by clinically significant events such as death, warranting retrospective data analyses) or the identification of a gene defect responsible for an earlier observed phenotype. Then, the same research group usually identifies the disease in an additional, albeit limited, number of patients and/or families. Other centers may confirm the original findings in a limited cohort of patients as well, who then initiate small, center-biased case series with relatively short follow-up. Such series inevitably include different genotypes and clinical presentations compared to cohorts from other centers, which may limit the comparability of data and outcomes between studies. As time progresses, clinical follow-up of patients with the respective disease lengthens, enabling researchers to conduct again a case series, yet with longer follow-up, by which they are potentially able to focus more on hard clinical endpoints. Such studies however, do not overcome the single-center (or, at least, the few centers) approach and the inherent biases. We feel that it should be acknowledged that at this stage the insights in the clinical aspects of the rare disease frequently arrive at a plateau phase of the ‘learning curve’. In order to then progress scientifically, further knowledge can be, and frequently is, obtained by more fundamental research on the mechanisms and pathophysiology of the identified defect. Examples of subsequent fundamental studies in the PFIC spectrum include those that assessed to what extent the genotype of

the *ABCB11* mutation (PFIC type 2) affected transport capacity of its gene product, the Bile Salt Export Pump (BSEP), or to what extent the genotype affected the amount of protein reaching its correct cellular locus (Folmer et al., 2009; Paulusma et al., 2008; Pawlikowska et al., 2004; Strautnieks et al., 2008; Hayashi et al., 2005; Byrne et al., 2009). However, to obtain a more elaborate appreciation of the natural clinical history of the disease only two factors seem critical: large patient numbers and extensive patient histories, i.e. prolonged follow-up and at the same time avoiding any kind of bias and ensuring high quality data. Large patient numbers in a rare disease is only achievable through collaborations with members of other centers. Ideally, centers have followed the patients for a considerable period of time. Retrospective data collection can then ensure a long follow-up. Another benefit from joining forces, including researchers from other centers and/or countries to achieve a greater sample size, is the creation of a scientific platform of experts with diverse knowledge-areas. Such a platform will enrich discussions and collaborations, secondary to aggregating scientific and clinical views of experts on a particular disease. This is needed to fuel academic discussion, which should aim at identifying and addressing the most important clinical and scientific issues in order to improve the individual care of the patients. These issues could include the need for genotype-phenotype association studies, for example to elucidate indications and/or contraindications for specific drug or intervention targets for patients with specific genotypes. The multicultural differences in care, culture or ethnicity (not to forget social economic differences in healthcare) between sites and/or countries can shed light on potential outcome differences of the natural history of the disease. Also, in rare diseases there usually exists an unmet medical need. It may therefore be essential to assess in detail the phenotype in order to be able to adequately determine the effect of drugs or other interventions on phenotypic subcategories of patients.

1.3. Identifying the methods

Following the previously mentioned discussion concerning the most relevant clinical and scientific issues, we commenced by drafting a research protocol for the NAPPED initiative. In our experience and perhaps counterintuitively, it is essential to *limit* ambitions at this stage. Indeed, one should strive to tackle the most relevant clinical and scientific issues, yet if the protocol tries to cover too many of these issues, it may be hard to depict a clear direction to which the consortium is heading. Additionally, acquiring participants will likely be more difficult due to the anticipated amount of work that will have to be put in.

It is essential that during the early days of the consortium, the burden of work for participating centers is kept as low as possible. Joining the study group should be made easy. One should keep in mind that acquiring IRB approval, data sharing agreements and retrieving patient data will likely be the three most labor-intensive tasks for new participants. While the first two are largely dependent on local legislation, the third depends on the methods by which data are captured and stored. Clear case report forms (CRFs) with self-explaining variables should be constructed. It is critical for early and qualitative output that the filed data is of good quality, in order to be able to answer the previously formulated research questions. Ideally, online data capturing systems with audit trails (we chose to use REDCap (Harris et al., 2009)) are used to ensure safe and central storage of global data. Expert knowledge on IRB and data transfer needs to be present within the organizing team. Audit trails are needed to ensure transparency. In Supplementary file 1 we incorporated our initial CRF, which was used in the starting phases of our consortium. This could function as a backbone for a simple and clean CRF, which formed the basis of the first years of the consortium.

1.4. Identifying the clinicians, the patients and their data

Once we had created a clear scientific framework, participating centers were recruited. By using our professional network and

previously published literature, we created a list of potential participants. We thought it was especially important to identify ‘key players’. Particularly, we have invested time and effort to communicate with the ‘pioneering’ centers and investigators who have previously published on the subject, in order to get them on board for this initiative in the early stages of setting up the consortium. With these investigators we set up a ‘Steering Committee’, which from the start was involved in major decisions regarding research questions, redrafting the CRFs, abstracts, papers and other forms of research output. We feel it is essential to limit the number of Steering Committee members in order to ensure comprehensible communication and meetings. We have had very good experience with a Steering Group size (in NAPPED and in other initiatives) of 4–7 persons.

For the acquisition of centers, we have welcomed from the start every center/doctor who had followed any patient with the respective diseases during childhood. Patients had to express a clinical PFIC phenotype and preferably be confirmed with a genetic diagnosis. We are convinced that it is important not to be picky in terms of the number of patients that centers can contribute to the dataset: for these (ultra) rare diseases, every patient counts – a clear diagnosis is, however, essential for first analyses. We believe that one should create a ‘coalition of the willing’ and even with low patient numbers, centers or clinicians can contribute greatly to the consortium, perhaps not so much in terms of large amount of patient data, but rather in terms of networking capabilities, scientific contributions and recruitment of new participants and high quality data. Of note, we have limited the analyses of our first papers and abstracts to patients with a genetically confirmed diagnosis in order to be able to adequately establish genotype-phenotype associations. In future initiatives we will additionally attempt to address the patients without (complete) genotypic information.

Through their own network or through that of novel entering sites, the consortium should continuously strive to retrieve contact information (through already participating centers) of potential new sites that could join the initiative. Acquisition of new centers never stops, neither does follow-up of included patients and data quality assessment. While the professional network of the team allows identification of potential participants, it is important that the team make an effort to expose its novel initiative towards other centers. This can be done at, for example, monothematic conferences related to the rare disease, where they can pitch their aims and methods. Also, they should host investigators’ meetings during conferences and invite candidate investigators to that particular meeting.

From the early stages onwards, the leading team should be accessible, be that through email, through face-to-face meetings and through the earlier mentioned newsletters. If applicable, a PhD-candidate or study coordinator could be appointed as primary contact person. The PhD-candidate or study coordinator should provide opportunities for participants to have (digital) walkthroughs through the protocol and data capture system. The PhD-candidate should ensure that the quality of the entered data is of sufficient quality. Obviously, a PhD-candidate is likely to benefit him/herself from ample and proper data inclusion, because this improves subsequent data analysis and helps to provide scientific output. This on the other hand ensures success of the network – the PhD-candidate needs to finish within a fixed time-frame.

Finally, in the early stages, it should be realized that retrieving funding comprises a vital part of setting up a consortium. Expenses can include, for example, honoraria for expert data management and analysis staff and organization of investigator’s meetings. Funding may be acquired via academic institutions and professional societies, yet pharmaceutical companies could also be approached for unrestricted research grants. In rare diseases there usually consists an unmet medical need and particular pharmaceutical companies may be exploring novel pipelines for the respective (orphan) disease. For clinical trials and registration of the drug, it is essential for the pharmaceutical company that the natural history and (surrogate) endpoints are, to a certain extent, established. Natural history studies are usually needed to

establish these, in which the consortium may be academically interested; a win-win partnership.

1.5. Essential first years

The first years are defining the success of the consortium in the years thereafter. Once a considerable number of centers is participating and a sufficient amount of (qualitatively good) data has been entered into the data capture system, we feel that it is essential to provide scientific output as soon as possible. Logically, this should not come at the cost of quality. Speed is of the essence, however, since it will keep momentum, keep the members of the consortium motivated for future work and lastly, it will increase exposure to the scientific community which in turn will make it attractive for other health care professionals and centers to join the consortium. Output could consist of abstracts for (annual) international meetings, manuscripts in peer-reviewed journals, presentations of preliminary data at investigators’ meetings and of newsletters in which important news and/or data can be communicated towards the membership. We stress that quick output of good quality can only be realized if limited, succinct research questions and CRFs had been created in previous stages, which we discussed above. Apart from speed, inclusivity is important. Every center that has contributed data should be rewarded, for example in terms of authorship(s). The steering group may want to define to what extent a center is granted authorship to more than one individual per center, for example if that center has contributed a significant, above average proportion to the already aggregated data.

1.6. Evaluating the first years and setting the course for the upcoming years: from start-up towards consolidation

While the consortium continues to answer its primary research questions, plans for the following years should be drawn. These plans should include evaluating the previous years and answering more in-depth research questions in the following. During the evaluation of the first years, the consortium should critically revise if the primary research questions have been answered, and if not, what is needed to do so. The consortium should also focus on answering more in-depth research questions in future initiatives. The consortium as a whole should be included in this orientation, for example during investigators’ meetings. Also, centers should be able to pose new projects, which, after approval by the Steering Committee and the membership, they then can (co-)supervise as a principal investigator. These measures will not only keep the consortium motivated, it will also stimulate the development of novel projects and broaden the base of the whole initiative.

It should be realized that, for more detailed questions, additional data are needed. Not only in terms of quantity, yet also in terms of parameters that had not been collected in the first CRFs (since initial CRFs had been kept as simple as possible). Based on the limited data set, specific patient cohorts may be identified on which a more in depth, separate analysis could be initiated with a specific CRF. As stated above, inclusion of new centers should be continued at all times. In addition, it seems valuable if the team organizes a follow up rounds of data collection for the centers that had contributed data in the early stages. In case of retrospective data acquisition, follow up rounds provide opportunities to lengthen the follow-up of the already included patients and thus to obtain more solid endpoints. Finally, quality control measures should be installed, to guarantee proper data inclusion and the validity of the data. It seems realistic that some form of auditing needs to be developed when the consortium moves from its “start-up” towards a more consolidated status.

1.7. Key points and conclusion

In a relatively short period of time, the NAPPED consortium has been successful in creating a global network of clinicians focused on two rare

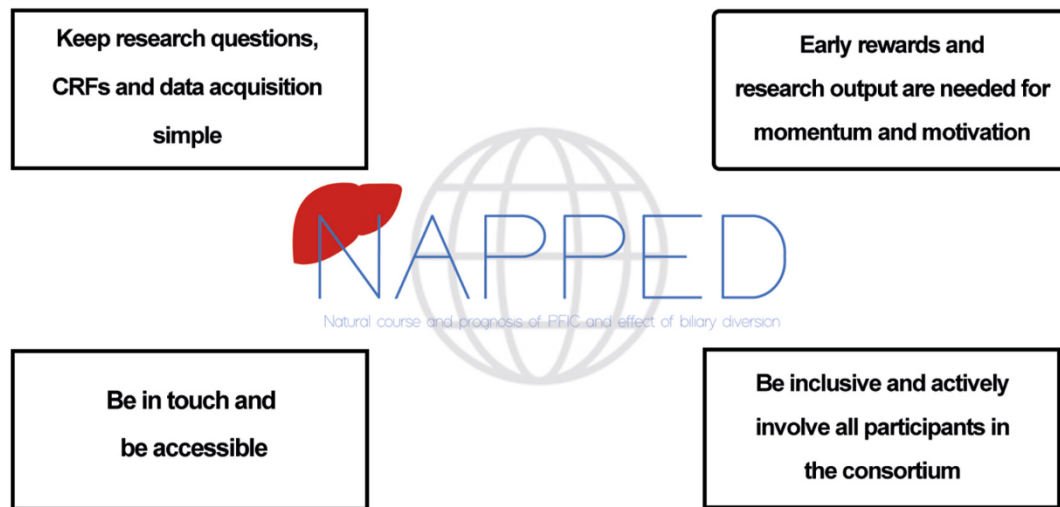


Fig. 2. Concise overview of key lessons learned.

genetic liver diseases in the PFIC spectrum. By doing so, after only three years, the largest genetically defined cohorts of severe BSEP and severe FIC1 deficiency have been established. The collected data allowed for drawing important conclusions which have impacted the clinical care for patients suffering from the diseases. We feel that some key points can be taken from our experience with the NAPPED consortium. Moreover, we feel that it is important to share them with the scientific community in order to benefit future initiatives. Fig. 2 provides a concise overview of the following points.

First, it is essential to ‘keep it simple’ from the start. Research questions, CRFs and data acquisition should be limited and clear, in order to stay focused and to keep the workload relatively low for new participants. At later stages, one can go into more detail. Secondly, early rewards and research output are needed to keep momentum and to keep the consortium motivated. Quick output can only follow if a clean and simple research design was created in the early stages. Thirdly, as the leading team, it is important to be in touch and to be accessible, be that through email, through face-to-face meetings and/or through newsletters. Ideally, a study coordinator or, perhaps even better, a PhD-student involved in the project should be appointed as primary contact person (if applicable). Lastly, be inclusive and actively involve all participants in the course of the working group.

We hope that we hereby stimulate those that are starting or planning to start a global study group to improve the care for a rare (genetic) disease. We feel that the lessons we have learned are transferable to rare diseases in general, since pitfalls are generally resulting from the rarity of such diseases. The information herein can hopefully function as a tool to successfully initiate and thereafter lead an academic consortium. Finally, we want to emphasize that such a consortium is critical for personalized medicine, which includes providing precise counseling and adequate treatment. Also, it is essential for setting up clinical trials for investigating generic drugs and personalized therapies. We aim to start using NAPPED data for the design of new trials by framing inclusion, exclusion and sample sizes based on estimates from our database. Our cohort may also be used as a placebo group, or external control arm, versus an active arm in the clinical trial itself.

We want to thank and acknowledge all the patients and/or their parents that have contributed their data to NAPPED, as well as all the participating sites for their efforts. Also, we thank the University of Groningen (MD/PhD scholarships), the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN, Networking Grant, 2019), the United States National Institutes of Health (several grants) and Albireo and Mirum Pharmaceuticals (unrestrictive research grants) for their financial support. Finally, we wish to express our

gratitude to the (other) members of the NAPPED Steering Committee (Richard Thompson, Irena Jankowska, Benjamin Shneider, Etienne Sokal) and the principal investigators of all the participating centers for all their efforts.

NAPPED is continuously looking for new participants. Interested centers are very welcome to contact NAPPED by sending an email to a.felzen@umcg.nl or h.j.verkade@umcg.nl.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejmg.2021.104245>.

Author Contribution

Daan B.E. van Wessel; Conceptualization, Methodology, Writing – Original draft, Visualization. Emmanuel Gonzales; Conceptualization, Methodology, Writing - Review & Editing. Bettina E. Hansen; Conceptualization, Methodology, Writing - Review & Editing. Henkjan J. Verkade; Conceptualization, Methodology, Writing – Original draft, Supervision.

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