MEDICAL UNIVERSITY – PLOVDIV

FACULTY OF PUBLIC HEALTH

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POST-MARKETING ACCESS TO GENE THERAPIES

A B S T R A C T

of a dissertation thesis for awarding
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The dissertation is presented on 187 pages and is illustrated with 10 tables, 47 figures and 3 appendices. The bibliography includes 241 literary sources – 21 in Cyrillic and 220 in Latin.

The doctoral student was given the right to defend by order No. P -1017 / 28.02.2025. The dissertation is scheduled for defense before a scientific jury composed of:

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The public defense of the dissertation will take place on May 22, 2025 at 11:00 AM in the Second auditorium of the Auditorium Complex, Medical University – Plovdiv.

The materials for the defense are available at the Scientific Department of MU-Plovdiv, 15A Vasil Aprilov Blvd. and on the university's website - https://mu-plovdiv.bg/.

CONTENTS

LIST OF ABBREVIATIONS USED

GT	Gene Therapy
EU	European Union
BDA	Bulgarian Drug Agency
MP	Medicinal Product
ATMP	Advanced Therapy Medicinal Products
MH	Ministry of Health
NHIF	National Health Insurance Fund
NCPRMP	National Council for Prices and Reimbursement of Medicinal Products in Bulgaria
HTA	Health Technology Assessment

INTRODUCTION

The idea of "living drugs" that treat the immediate cause of the disease, rather than its symptoms and complications, has existed since the discovery of recombinant DNA as a carrier of heredity, physiological functions and regulation in cells. A large part of diseases is a pathological change in one (e.g. hemophilia) or several genes (e.g. oncological diseases).

Therapeutic nucleic acid medicinal products are a subset of medicinal substances that are relatively new to clinical practice. Internationally, there are different definitions and classifications of this type of medicinal product - advanced therapy medicinal products (ATMPs) within the European Union (EU), gene and cell therapies in the USA, regenerative medicine products in Japan, and others. Different definitions and legal frameworks, as well as healthcare systems, also set different criteria and mechanisms for authorisation, distribution and patient access.

The mechanism of action of gene therapies (GTs), as well as their indications for rare diseases, severely limit the scale of ethically acceptable clinical trials. This leads to insufficient data on efficacy and safety at the time of application for marketing authorization of the products. At the same time, GTs are intended to treat severe and disabling genetic diseases, for which there are often no alternative treatments. The high cost of therapies with the potential for lifelong cure with a single dose administration is a serious challenge for patient access. With prices starting from tens of thousands and reaching millions of dollars, the therapies are practically unattainable for the majority of those in need without funding from public or private funds.

Health regulators recognize the importance of GT innovations and therefore strive to find a balance between the uncertainty of treatment outcomes and the high budgetary burden that their financing brings. Adapted criteria for health technology assessment, controlled market entry, new methods of public reimbursement of treatments by sharing financial risk between payers and manufacturers, as well as regulated alternative methods of patient access, sometimes before obtaining a marketing authorization, are used.

By the end of 2024, 19 advanced therapy products had marketing authorisation in the EU. Given the fragmented European market and specific

legislation in each Member State, access to GT by citizens of different European countries is highly unequal.

To date, there is no advanced therapy product in Bulgaria that is included in the Positive Drugs List, therefore the only options for patient access are under Ordinance No. 2 of March 27, 2019 or through Ordinance No. 10 of November 17, 2011. Both ordinances implement individual access to treatments - through individual delivery of medicinal products (MP), according to the authorization of the Bulgarian Medicines Agency (BMA) and the decision of specialized competent committees. At the time of the study, there was no active program for compassionate use of ATMP in the country.

Given the scientific development in this field of medicine, the entry of GTs into the Bulgarian market, although delayed, will be inevitable in the near future. Following the above, in this dissertation an algorithm for public financing of GT treatments is proposed, which is consistent with the preferences and attitudes of two of the stakeholders - medical specialists and patients, as well as relatives of pediatric patients who can be treated with them. In terms of establishing an optimal economic model for financing, the study participants were asked to evaluate methods, successfully applied internationally for financing GTs.

AIM AND OBJECTIVES

1. Aim of the study

Establishing an optimal model of patient access to GTs in Bulgaria with a view to balancing the economic burden and ensuring the effective spending of public funds for healthcare, on the one hand, and meeting the expectations and needs of medical specialists and patients, on the other.

2. Objectives

To achieve the set aim, the following objectives have been defined:

2.1. Survey of the opinions, attitudes, expectations and main considerations of medical professionals regarding treatment decision-making and public funding of GTs.

2.2. Research and analysis of the opinions, attitudes, expectations and main considerations of patients and their relatives regarding treatment decision-making and public funding of GTs.

2.3. Creation of a pilot model for reimbursement of GT treatment based on the researched expectations and benefits, the economic burden and the satisfaction of the main stakeholders – medical specialists, patients and their relatives.

MATERIALS AND METHODS

1.1. The subject of the study is post-marketing patient access to GTs.

1.2. The subject of observation are the conditions for patient access, the criteria and methods for reimbursement of GTs in Bulgaria according to medical specialists and patients and their relatives.

1.3. Units of observation are medical experts and adult patients with hemophilia or parents of pediatric patients.

1.4. Observed variables

1.4.1. Questionnaire for medical professionals.

Qualitative and quantitative factorial variables: sex, age, currently practiced medical specialty, professional experience in years, presence of clinical experience with GTs.

Qualitative and quantitative outcome variables: main source of information for GTs, value of the minimum threshold of treatment success among patients for a recommendation/decision for GT treatment, importance of disease progression as a factor for treatment reimbursement, degree of importance of criteria for priority reimbursement of GT treatments in chronically ill patients and pediatric patients, importance of quality of life and survival, importance of long-term clinical safety and effectiveness, assessment of periodic contributions related to achieving and maintaining a clinical outcome as a reimbursement method, assessment of periodic contributions until the occurrence of an adverse event as a reimbursement method, assessment of a one-time full payment after treatment as a reimbursement method, significance and grading of various indicators of successful treatment in the absence or in the presence of a therapeutic alternative, value of the minimum duration of therapeutic response as an indicator of treatment success, value of the optimal period of long-term follow-up of patients, frequency of data collection and institution for data collection and analysis from long-term follow-up.

1.4.2. Questionnaire for adult patients and relatives of pediatric patients.

Qualitative and quantitative factorial variables: sex, age, respondent category, education, marital and employment status, age at diagnosis, type

and severity of the disease, type of treatment at the time of the study, frequency of bleeding, joint disorders and complications identified as a result of the disease among the patients;

Qualitative and quantitative outcome variables: assessment of the results of the current treatment, level of awareness of GTs, main source of information about GTs, desire to change or replace the current treatment, discussion with a specialist of options and relevant decisions for GT treatment, value of the minimum threshold of success of GT treatment as a factor for their reimbursement, determination of readiness for the administration of GT as a treatment in conditions of insufficient evidence of long-term effectiveness and safety, degree of agreement for full reimbursement of treatments in conditions of insufficient evidence of long-term effectiveness and safety, assessment of periodic contributions for achieving and maintaining a clinical result as a reimbursement method, assessment of periodic contributions until the occurrence of an adverse event as a reimbursement method, assessment of a one-time full payment after treatment as a reimbursement method, value of a minimum time period without typical manifestations of the disease as a factor for the success of GT treatment.

1.5. Location of the study

The study was conducted using three questionnaires - for medical professionals, for adult patients, and for relatives/parents of pediatric patients. They were distributed via links to a Google Forms form.

1.6. Duration of the study

The survey was conducted between June 2023 and September 2024.

1.7. Research bodies

The study was conducted with the personal participation of the doctoral student, under the guidance of the supervisor.

2. Methods

2.1. Sociological methods

A. Questionnaire for medical professionals

The questionnaire was distributed among medical specialists from various medical fields. The specialties of the experts included in the study were selected according to the currently authorized GT products and the relevant medical specialties that have an overview of the specific pathologies and treatments. The survey for medical specialists was of a closed-ended type - links with invitations to participate were sent by the doctoral student to the publicly available email addresses of specialists in the relevant medical specialties in the country, through the official websites of university hospitals and medical institutions, as well as medical centers. In order to collect more responses, there were biweekly electronic reminders to complete the survey. The survey data was collected completely anonymously and stored on the Google Forms platform.

The survey was conducted between July and September 2023.

B. Questionnaires for adult patients and for relatives/parents of pediatric patients.

For the purposes of the study, a target group of patients with hemophilia was defined - a disease for which GT products are authorized for use and there is an alternative treatment. Given that the decision to treat with GT is made with the consent of adult citizens and in the interest of the number of results obtained, a questionnaire for relatives and parents of pediatric patients was also adapted during the study. The patient survey was open to all patients with hemophilia who wished to participate and was distributed with the assistance of the Bulgarian Hemophilia Association and the Clinic of Pediatric Clinical Hematology and Oncology at the University Hospital "Tsaritsa Yoana - ISUL". Invitations to participate were also published on the Facebook page of the Institute for Rare Diseases in Plovdiv. The survey data was collected completely anonymously and stored again in the Google Forms application. The information that was collected did not require the entry of personal data and was conducted in conditions of complete anonymity. Participation in the study was completely voluntary on the part of the respondents and did not affect changes in treatment, care, or any clinical data and research, therefore permission from the Scientific Ethics Committee was not necessary.

The survey was conducted between January and April 2024.

2.2. Statistical methods

The collected primary information was checked, entered, coded and processed using specialized statistical software IBM SPSS Statistics v.18.00, as well as Microsoft Office Excel, where applicable.

The level of statistical significance was set at $p < 0.05$.

The following statistical methods were used:

1. Distribution analysis – for calculating mean values and dispersion indicators of quantitative variables;
1. Alternative analysis – for calculating the relative share of qualitative variables;
2. Nonparametric analysis – for studying associations, relationships and dependencies between the studied variables;
3. Fisher's exact test, λ test of Klomogorov-Smirnov, Kruskal-Wallis test , Mann-Whitney test;
4. Graphical analysis – to visualize the observed processes and phenomena and illustrate the existing patterns (Microsoft Office Word, Microsoft Office Excel).

RESULTS AND DISCUSSION

I. Survey of the opinions and attitudes of medical specialists regarding the conditions of patient access and the criteria for reimbursement of GTs in Bulgaria

1. Socio-demographic data about the participants

49 fully completed questionnaires were received, there was no incorrectly completed survey.

The participating medical specialists ranged between 31 and 85 years of age (mean age: 57.16± 11.78 years), of whom 59.2% were female (n=29) and 40.8% were male (n=20). The largest number of specialists in the study had a specialty in oncology and hematology, as well as pediatric oncohematology (Fig. 1).

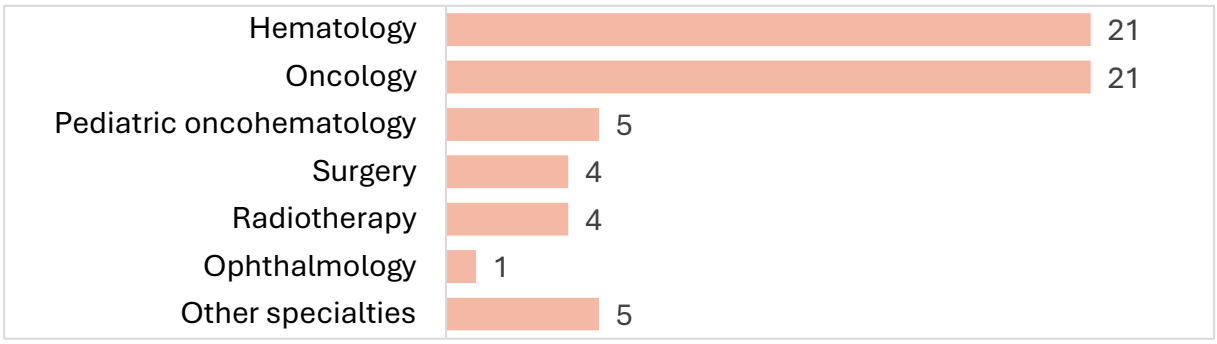

Fig. 1. Distribution of medical specialties currently practiced by respondents.

2. Professional experience and experience with the administration of GTs

The average length of professional experience among respondents was 29.61 ± 12.78 years. A significant proportion of all 49 respondents had clinical experience with GTs (n=19; 38.8%), the experience with GTs being mostly the result of clinical activity and patient follow-up (28.6%), as well as through clinical trials with humans (24.5%), and significantly less was acquired through specializations (8.2%).

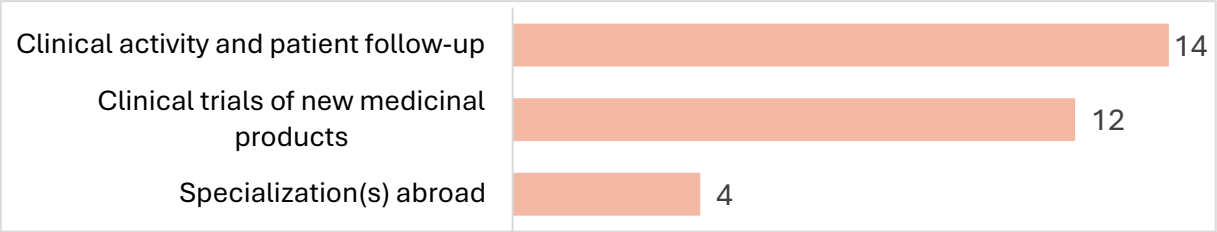

Fig. 2. Distribution of respondents according to the method of acquiring clinical experience with GTs (n=19).

Clinical experience with GT treatments is an important factor that deserves further study with respect to its significance for specialists' attitudes and assessment of innovative treatments. The opinion of representatives of health regulators who are decision-makers on public funding should be influenced not only by scientific evidence of effectiveness, but also by the clinical experience with such products of expert health technology assessors.

3. Sources of information about new GTs

When asked about the main source of information about GTs approved for marketing in their specialty, respondents most often cited medical databases for scientific articles and studies (n=38; 77.6%), with representatives of the pharmaceutical industry as the second most common source of information (n=24; 49%). Significantly fewer respondents cited health authorities (n=12; 24.5%) and professional organizations (n=11; 22.4%) as the main sources of information about new therapies.

Although they agree on the most frequent source of information, the groups of specialists with and without experience with GTs differ in terms of medical databases as the main source of information (p=0.03). In the group with clinical experience with GTs, 94.7% of the specialists indicated this answer, while in the group without clinical experience, the rate was 66.7% of all respondents in the group. No statistically significant differences were found for the remaining proposed sources of information about GTs between the responses of the two groups (Fig. 3).

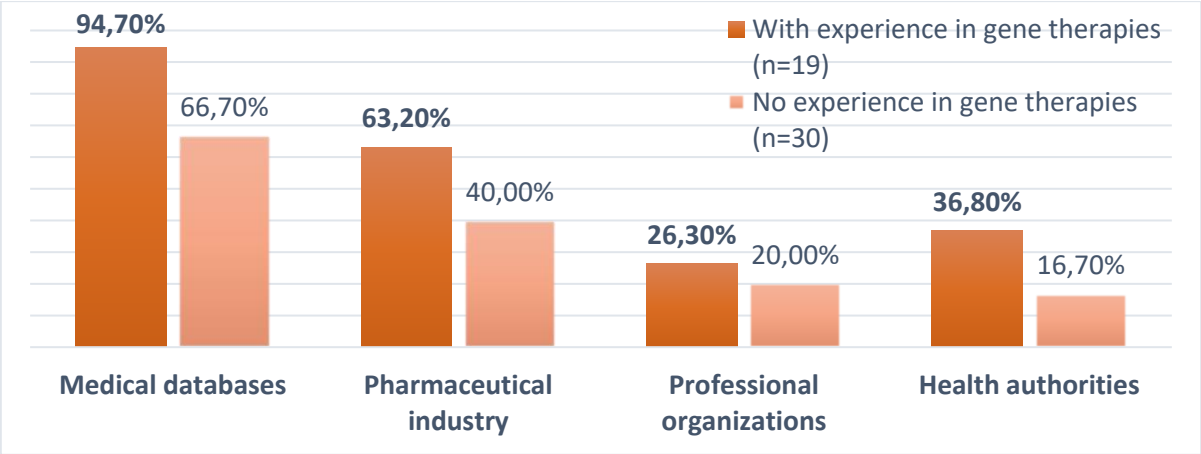

Fig. 3. Distribution of preferences for main sources of information in the subgroups of medical specialists.

4. Establishing a minimum required threshold for treatment success

Determining the criteria for treating patients with GTs is a fundamental part of making a decision to carry it out, which helps to predict future healthcare costs. Of paramount importance in this sense, according to the specialists, is the degree of clinical effectiveness or success of the treatments, to which it makes sense to recommend them to new patients at all.

The largest number of respondents from the sample are grouped in the two extremely lowest and highest success rates. Twenty out of 49 respondents indicated that they would recommend the therapy to new patients with a proven success rate of over 50% (n = 20; 40.8%). There is a clear difference in opinion regarding the minimum proven effectiveness of new treatments between specialists with real clinical experience with GTs and those without ($p = 0.08$), but this difference is not statistically significant due to the small sample.

Table 1. Distribution of medical specialists according to their choice of the minimum required threshold for success of GT treatments (n = 49).

Treatment success rate	Number of respondents	Clinical experience with GTs	Number of respondents who would recommend GTs	Percentage share
Over 50%	20	Yes	12	63.1%
		No	8	26.7%
Over 60%	3	Yes	1	5.3%
		No	2	6.7%
Over 70%	8	Yes	2	10.5%
		No	6	20%
Over 80%	18	Yes	4	21.1%
		No	14	46.6%

Respondents with clinical experience with GTs, regardless of the mode of acquisition, are clearly more likely to recommend the therapies even at lower proven rates of effectiveness. The reason for this could be their preparedness for working with such therapies - the experience gained and the associated expectations for their effectiveness on patients, including possible adverse effects (n=12; 63.1%). At the same time, specialists without clinical experience with GTs rely on the higher success rates and safety of the treatment being administered, with the highest support for treatments with over 80% success rate (n=14; 46.7%).

When grouping the data for the minimum threshold of treatment success, a statistically significant difference is noted between the group of specialists with clinical experience with GTs, who support treatments (n=13; 68.4%) under conditions of proven success rates in the range of over 50-60%, and respondents without clinical experience with GTs, supporting the same success rates (n=10; 33.3%; p=0.02).

The obtained mirror results clearly show clinical experience with GTs as a factor in terms of their frequency of use in a clinical setting with access conditions.

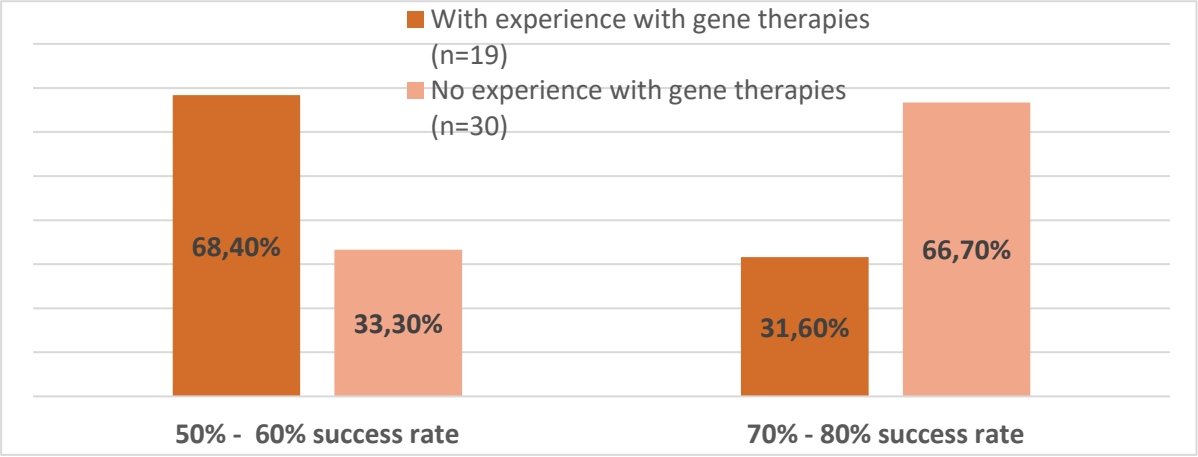

Fig. 4. Minimum required success thresholds (grouped data).

5. Importance of disease progression as a factor for reimbursement of therapies

Disease progression is an important criterion for determining the economic feasibility of a given treatment, as well as for decisions on reimbursement.

According to the respondents in the study, the progression or stage of the disease is rather not a determining factor in the decision to reimburse therapies, with opinions being divided almost equally (p=0.7).

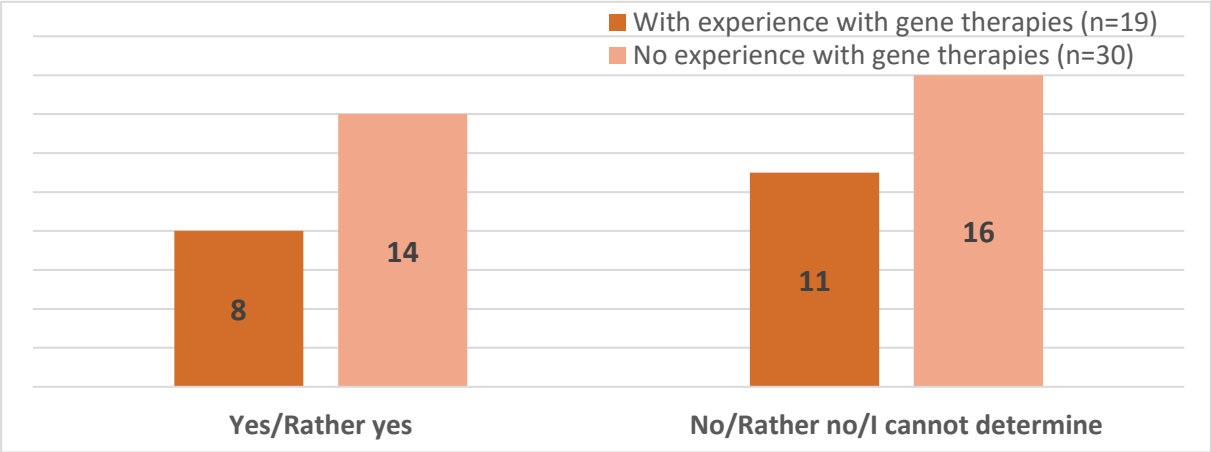

Fig. 5. Importance of patients' disease stage for reimbursement of GT treatment.

6. Determining criteria for priority reimbursement of GT treatments for specific groups of patients

The determination of specific priorities in the reimbursement of expensive treatments is a standard economic mechanism by which health authorities provide an opportunity for treatment to the most needy and/or vulnerable groups of patients while maintaining good financial predictability of health budgets. Therefore, for the purposes of the study, four hypothetical cases were presented to the specialists to rank the importance and appropriateness of the reimbursement of GT treatment in the presence of specific conditions - lack of alternative treatment (Scenario No. 1), after previous unsuccessful treatment (Scenario No. 2), in the presence of alternative treatment associated with multiple, long-term and difficult-to-tolerate procedures by the patient (Scenario No. 3) and in achieving better MP indicators compared to standard therapy (Scenario No. 4). The respondents determined the level of importance using a five-point ascending scale (with 1 being the lowest and 5 being the highest level of importance), and the possible scenarios were assigned to two groups of patients - with chronic diseases and for pediatric patients.

Table 2. Mean values obtained for the priority of reimbursement of GTs for the treatment of patients with chronic diseases under given conditions (n = 49).

	Mean value	Standard deviation
Scenario No. 1	4.10	1.42
Scenario No. 2	3.55	1.29
Scenario No. 3	3.24	1.22
Scenario No. 4	3.78	1.31

As expected, the highest importance is given to the reimbursement of GT with public funds in the absence of alternative treatment (4.10 ± 1.4). The scenarios with available treatment are ranked in order of importance as follows: with better indicators of the new treatment (3.78 ± 1.31), after unsuccessful treatment so far (3.55 ± 1.29) and with available alternative treatment associated with temporary and/or persistent decrease in patients' quality of life (3.24 ± 1.21), respectively. No statistically significant difference is found between the assessments of the different scenarios.

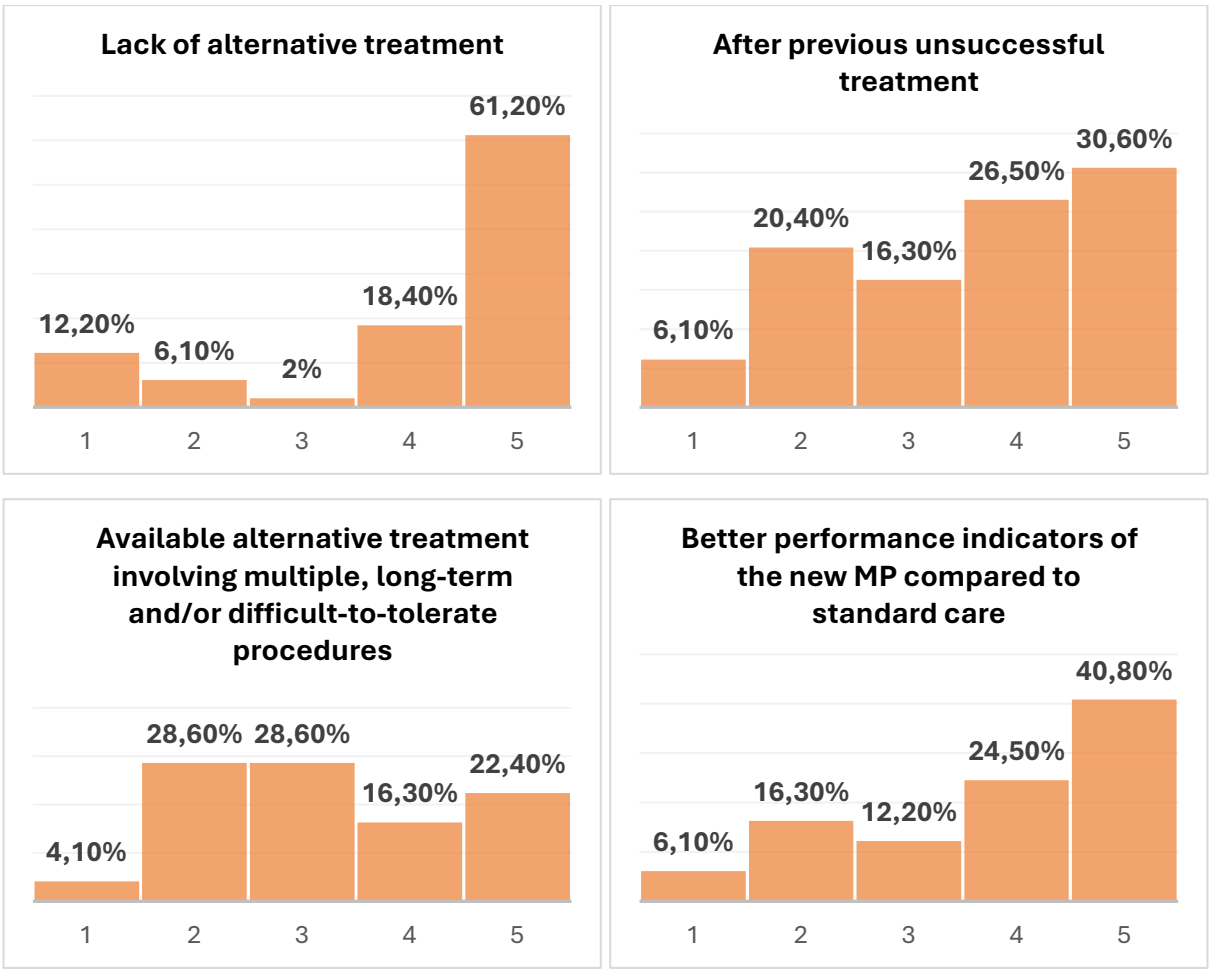

Fig. 6. Distribution of scores for priority of reimbursement of GTs for the treatment of chronically ill patients under given conditions.

The same set of scenarios, but referenced for pediatric patients, are distinguished by a higher mean priority value (Fig. 7). This is also expected given the importance of children's health as a socially significant priority and a kind of investment in the future.

Table 3. Mean values obtained for the priority of reimbursement of GTs for the treatment of pediatric patients under given conditions (n = 49).

	Mean value	Standard deviation
Scenario No. 1	4.14	1.53
Scenario No. 2	3.80	1.36
Scenario No. 3	3.51	1.34
Scenario No. 4	4.00	1.36

Here too, the patients' preconditions were ranked in the same order as for chronically ill patients. The distribution of scores for the given scenarios

is similar to that for chronically ill patients. A higher proportion of the respondents considered the lack of alternative treatments for pediatric patients to be the most important criterion for reimbursement (n = 36; 73.5%), with over half of the respondents also placing maximum priority under better treatment outcomes (n = 29; 59.2 %) as well. The results obtained support the importance of reimbursement for pediatric treatments, regardless of the conditions set for the proposed cases.

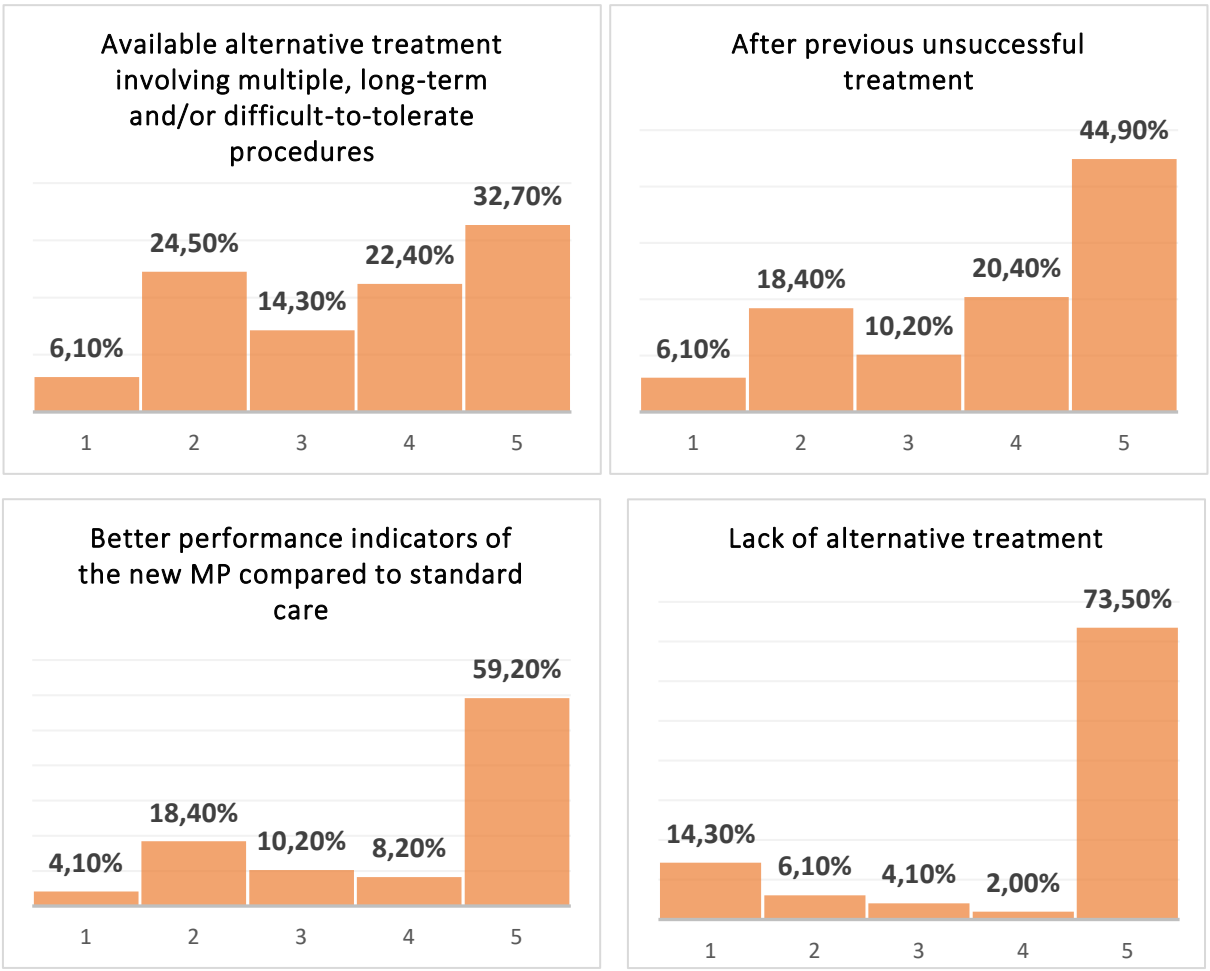

Fig. 7. Distribution of scores for reimbursement priority of GTs for treatment of pediatric patients under given conditions.

The importance assigned by the respondents differs in the subgroups according to clinical experience with GTs. The lack of alternative treatment, regardless of the patient group, as well as the improved indicators of GT treatment compared to standard care in pediatric patients are distinguished by scores above 4, while for the same options the group of specialists without GT experience reaches mean importance values below 3.99 (Fig. 8

and Fig. 9). No statistically significant difference was found between the listed groups.

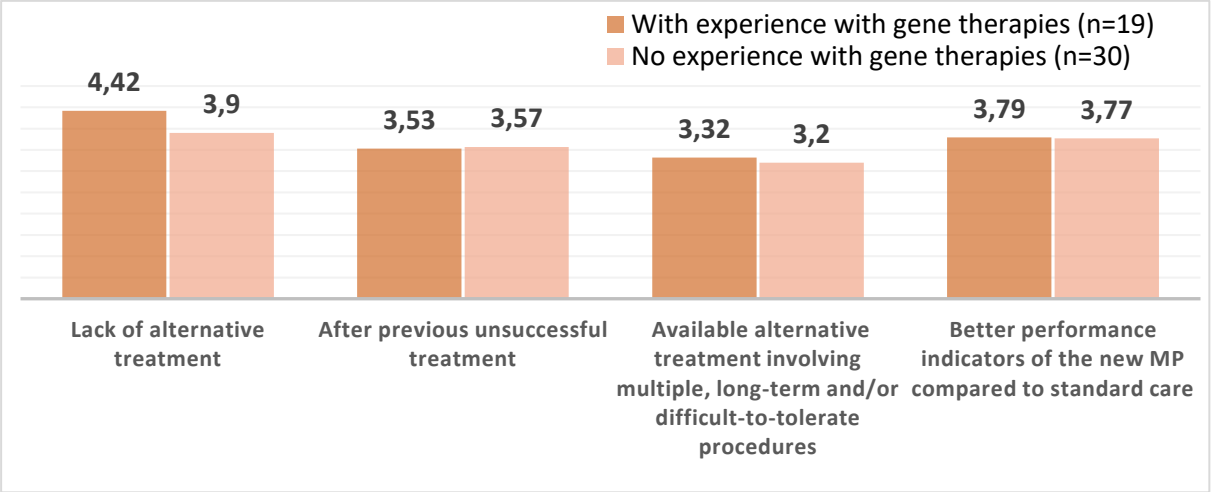

Fig. 8. Comparison of the mean values for reimbursement priority of GTs for the treatment of chronically ill patients in the subgroups of medical specialists.

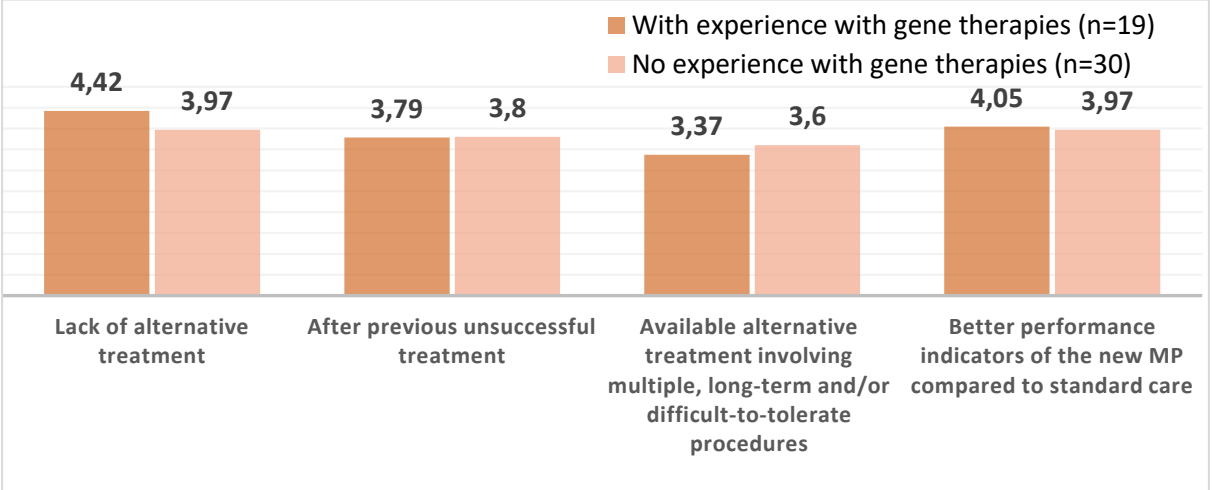

Fig. 9. Comparison of the mean values for reimbursement priority of GTs for the treatment of pediatric patients in the subgroups of medical specialists.

7. Assessing the importance of quality of life and survival rate as treatment outcomes

The present study compared the assessments of specialists regarding the need for reimbursement in the event of a hypothesis for a drug affecting either only the survival rate or only the quality of life of patients.

In the scenario where the MP only affects the survival rate, quite expectedly the majority of medical professionals give a positive opinion

about its reimbursement (n=37; 75.5%). However, a statistical difference is observed between the two subgroups of respondents (p=0.01).

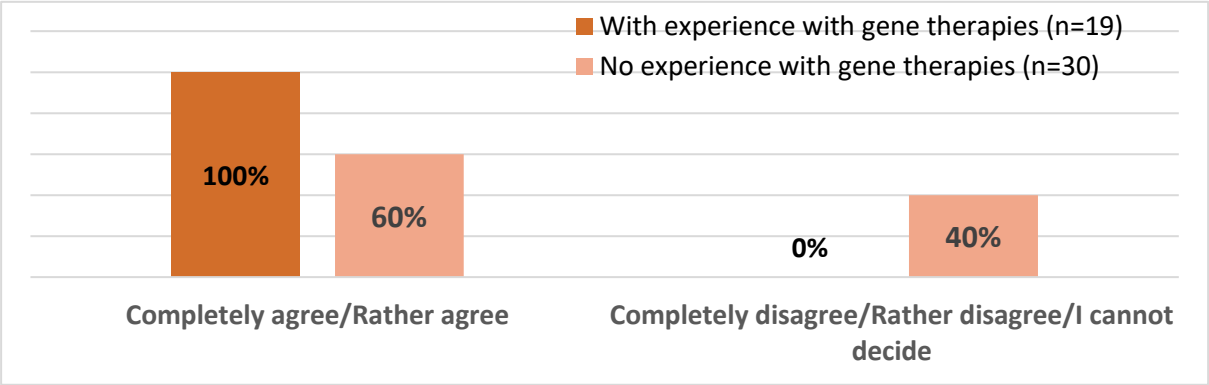

Fig. 10. Importance of survival rate as a factor for GT reimbursement.

In the other hypothetical situation, of an MP for GT, which affects the quality of life but does not change the survival rate of patients, the majority of the surveyed specialists again support reimbursement (n=37; 75.5%), but no significant difference was observed between the subgroups with and without experience with GTs (p=1).

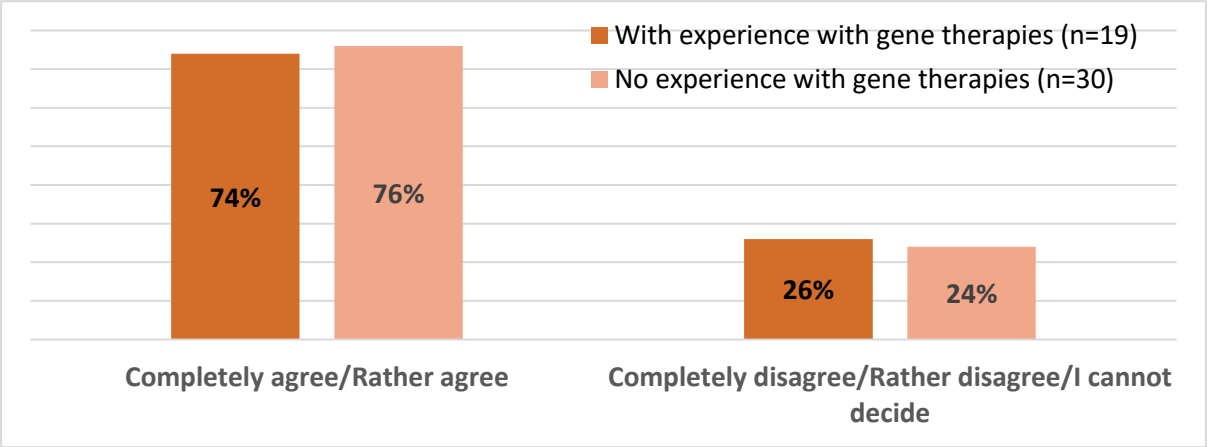

Fig. 11. Importance of quality of life as a factor for reimbursement of GTs.

Despite the small number of respondents in the sample (n=49), the lack of a negative answer in one hypothetical scenario is indicative and with an increase in the number of specialists with experience with GTs, the weight of the "survival" factor will logically increase. However, for patients on long-term treatment, with good or comparable survival rate to healthy individuals,

it is not a factor that has such a high weight. Quality of life displaces survival rate when the latter is satisfactory even with standard treatment.

8. Assessing the importance of long-term clinical safety and effectiveness

The study hypothetically presented the situation that regulators often find themselves in at the time of marketing authorization of products – the respondents determined their agreement to reimburse a GT, which affects survival and quality of life, but in the absence of sufficient evidence of long-term clinical safety and effectiveness. The majority of the respondents (n=36; 73.5%) gave a positive assessment of the agreement to reimburse effective GT products even in the absence of data on their long-term effect.

Although no statistical difference was observed in the agreement of the groups of medical specialists with and without experience with GTs (p=0.053), the proximity of the significance established in the sample to the statistical limit again emphasizes the importance of clinical experience with treatments as a factor shaping attitudes (Fig. 12).

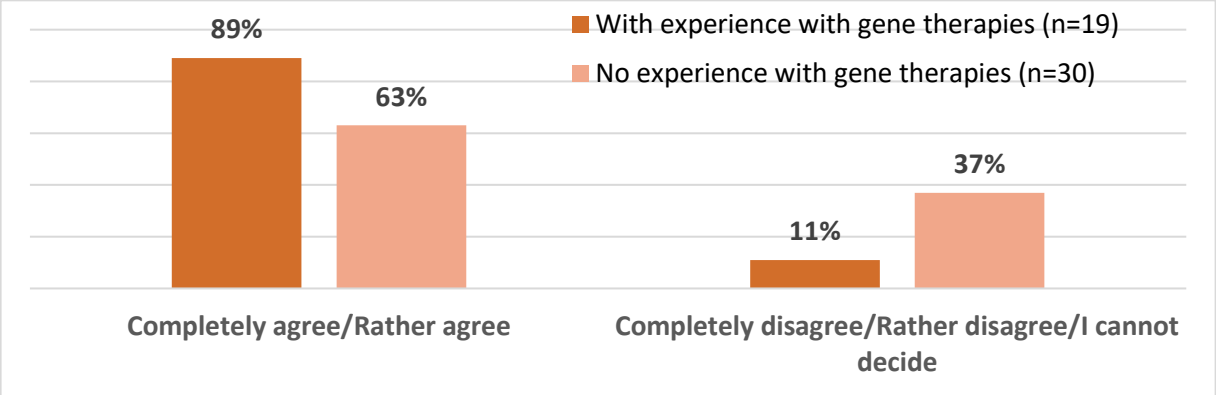

Fig. 12. Significance of the importance of the lack of sufficient data on long-term safety and effectiveness as a factor for reimbursement of GTs.

9. Reimbursement of GT costs in case of lack of treatment effectiveness

The high cost of GT treatments is a significant problem for their easier dissemination. Countries where treatments are reimbursed apply different ways of distributing the financial risk arising from the uncertainty of GTs' effectiveness and safety.

The majority of the 49 medical professionals surveyed agreed with reimbursement of costs from the pharmaceutical manufacturer in the event of ineffectiveness of GT treatments (n=28; 57.1%). Although there was no statistically significant difference in opinion between the subgroups of medical professionals with and without experience with GTs (p = 0.14), of interest is the higher prevailing share of disagreement in the subgroup of specialists with experience with GTs (n=11; 57.9%). In comparison, the share of disagreement in the group without experience is significantly lower (n=10; 33.3%). The observed difference between the two subgroups of respondents may be due to the established higher expected threshold of safety and, respectively, guarantee of effectiveness as a precondition for reimbursement of therapies, assumed by specialists without experience with GTs (Table 4).

Table 4. Distribution of agreement for refund by the pharmaceutical manufacturer/distributor in the subgroups of medical professionals (n = 49).

Degree of agreement	Number of respondents	Clinical experience with GT	Number of respondents	Percentage of subgroup
Completely agree / Rather agree	28	Yes	8	42.1%
		No	20	66.7%
Completely disagree / Rather disagree / I cannot determine	21	Yes	11	57.9%
		No	10	33.3%

10. Assessment of an appropriate GT reimbursement method

Uncertainty regarding the effectiveness and long-term benefits of treatments is gradually leading to an evolution in reimbursement methods. Most often, funding is postponed or spread over time, thus eliminating the high financial burden on the budget and/or is linked to the achieved therapeutic outcome, which addresses the effectiveness of treatments.

When asked to rate commonly used methods of reimbursement for therapies on a five-point ascending scale (5 being the highest, 1 being the lowest), the surveyed medical professionals in the study gave the highest average rating to funding tied to achieving or maintaining a predetermined clinical outcome (4.00 ± 1.09). Delayed payments tied to the occurrence of an adverse event were rated with an average rating of 3.43 ± 1.02, with the

option of the standard one-time full payment for the products after their administration being the lowest rated among the participants (3.16 ± 1.47).

Table 5. Mean values of the ratings for the proposed methods for reimbursement of GTs in the subgroups of medical specialists (n = 49)

Reimbursement method	Clinical experience with GTs	Assessment of the reimbursement method
Periodic payments linked to achieving and maintaining a clinical outcome	Yes (n=19)	4.00 ± 1.08
	No (n = 30)	4.00 ± 1.16
Periodic payments until an adverse event occurs	Yes (n=19)	3.47 ± 0.97
	No (n = 30)	3.37 ± 1.12
One-time full payment for the product	Yes (n=19)	3.33 ± 1.37
	No (n = 30)	2.89 ± 1.63

11. Expectations for the administration and outcomes of GT treatment

The minimum threshold of success is an important criterion, but no less important is how this success is measured as a real change in the health status of patients. For the purposes of the study, respondents assessed success with a five-point scale for hypothetical outcomes of GT treatment in two scenarios - in the absence or presence of alternative treatment for patients, respectively.

In the absence of alternative treatment, the highest success rate was achieved when significant improvement in clinical indicators and regression of the disease was demonstrated. Consensus was observed in both subgroups of specialists (p = 0.39) – 94.7% (n=18) of the subgroup of specialists with experience with GTs, as well as complete unanimity in the subgroup of specialists without experience (n=30; 100%) (Fig. 13).

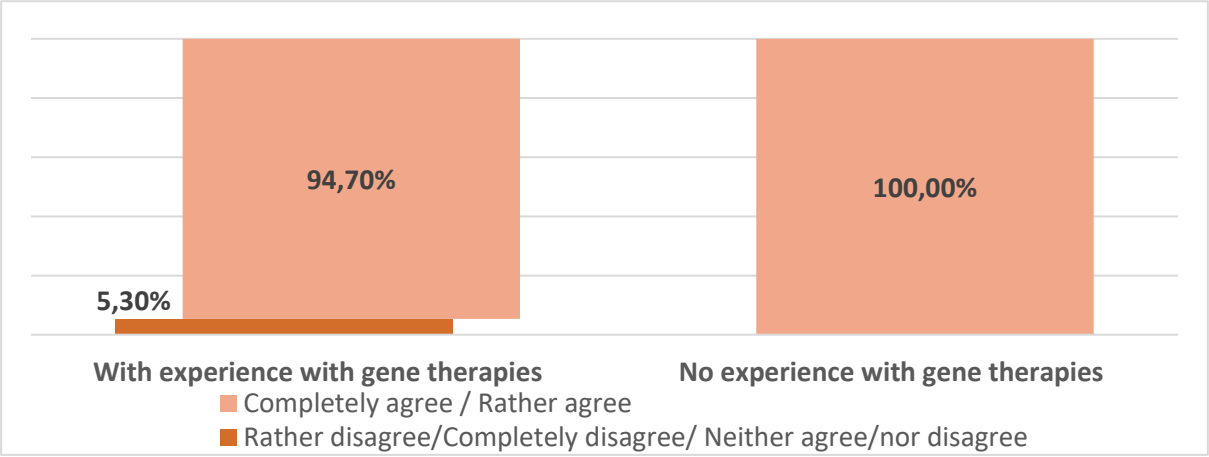

Fig. 13. Distribution of the degree of agreement on the success of GT treatment under the hypothesis of stopping the progression of the disease.

The same distribution of assessments by subgroups of respondents is also found in the case of the proposed hypothesis of stopping the progression of the disease as a factor indicating success (p =0.57). Both groups gave a high positive assessment for the hypothesis, with positive assessments given by 86.7% (n = 26) of the group of specialists without experience, and respectively 89.5% (n = 17) of the group with clinical experience with GTs (n = 17). There is a higher share of disagreement among respondents – over 10% of the responses in both subgroups (Fig. 14).

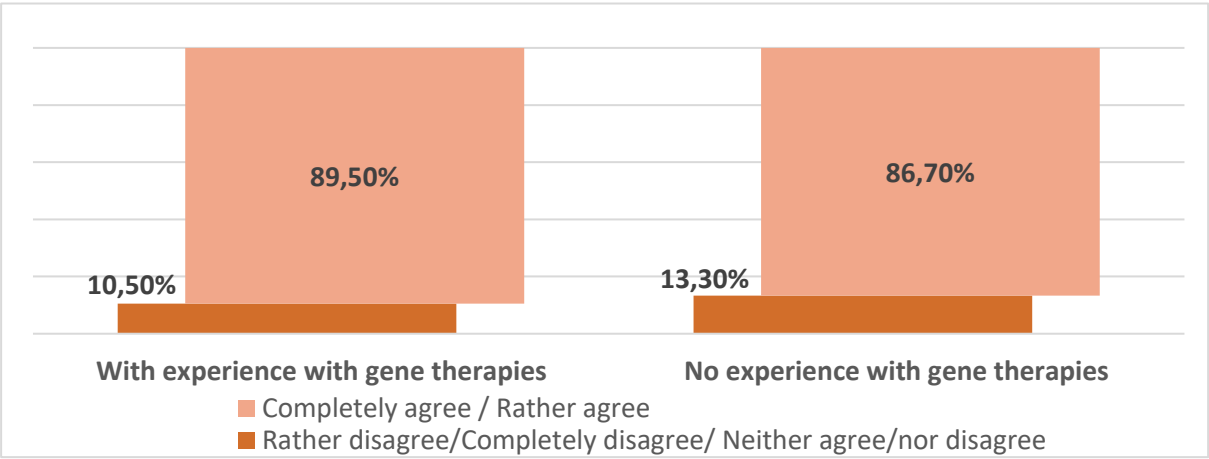

Fig. 14. Distribution of the degree of agreement for the success of GT treatment under the hypothesis of stopping the progression of the disease.

The last in terms of agreement among respondents is the hypothesis of successful treatment as any improvement in clinical indicators. Disagreement reaches 28.6% (n=14) of all 49 specialists surveyed (Fig. 15).

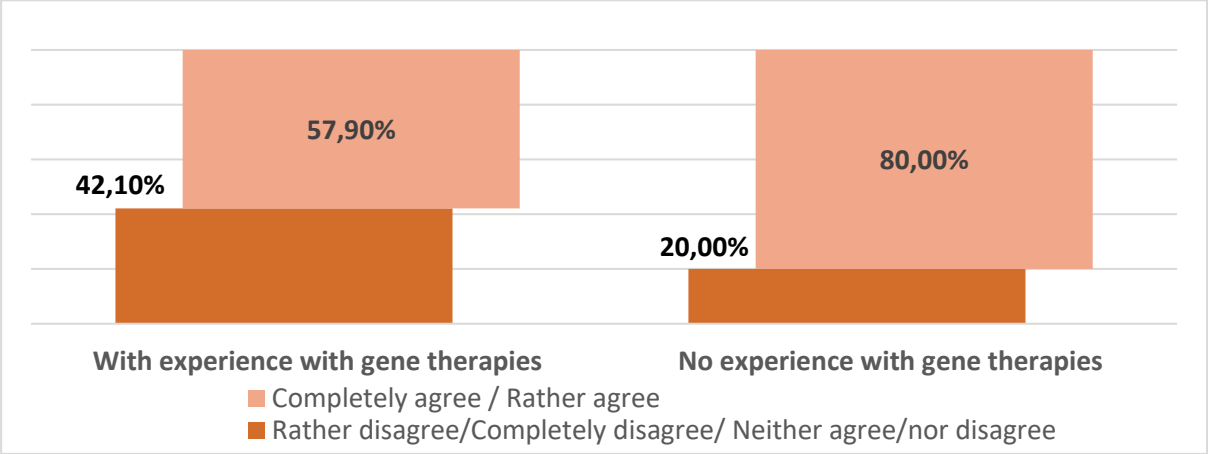

Fig. 15. Distribution of the degree of agreement on the success of GT treatment under the hypothesis of any improvement in clinical indicators.

The significant disagreement of medical professionals with clinical experience with GTs regarding any improvement in clinical indicators as an indicator of successful treatment, twice as high as that among professionals without experience, may be due to their expectations based on their experience with the clinical application of GTs.

Regarding the assessment of the success of GT treatment compared to complete cure in a scenario with an available alternative therapy/treatment course, regardless of the type of alternative, there was unanimous agreement among the specialists (n=46; 93.9%) regarding the hypothesis in which the results of GT treatment are summarized as “significant improvement of clinical indicators and regression of the disease” and there was no difference between the opinions of the group of specialists with and without experience with GTs (p=0.67). With a slightly higher percentage of disagreement about the effectiveness of GTs among the respondents is the hypothesis in which the treatment leads to a halt in the progression of the disease. Nearly a quarter of the respondents consider this option to be rather unsuccessful (n=11; 22.4%), and here too no statistically significant difference was found between the subgroups of specialists with and without experience with GTs (p=0.43). In third place in terms of the obtained success assessments is the hypothesis in which the treatment with GT improves the

clinical indicators of the patients above the expected ones compared to the results of the administration of the alternative therapy. Last in terms of agreement is the hypothesis of the success of the treatment with GT as “any improvement of the clinical indicators”, similar to the option without alternative treatment. More than half of the respondents with experience with GTs believe that this is not a sufficient indicator of the effectiveness of the treatment (n=10; 52.6%). The lower relative share of disagreement in the group of specialists without clinical experience with GTs – 20% in the absence of alternative treatment and 40% in the presence of alternative treatment, respectively, indicates a higher tolerance of the specialists in the group without experience with GTs regarding the outcomes of the administration of the therapies, especially in the absence of an alternative for the patients.

On the other hand, given the lower level of disagreement among specialists with experience regarding the same hypothesis without available alternative treatment (n=8; 42.1%), compared to the hypothesis with alternative treatment (n=10; 52.6%), it could be assumed that clinical experience with GTs leads to inflated expectations for the outcome of the treatments.

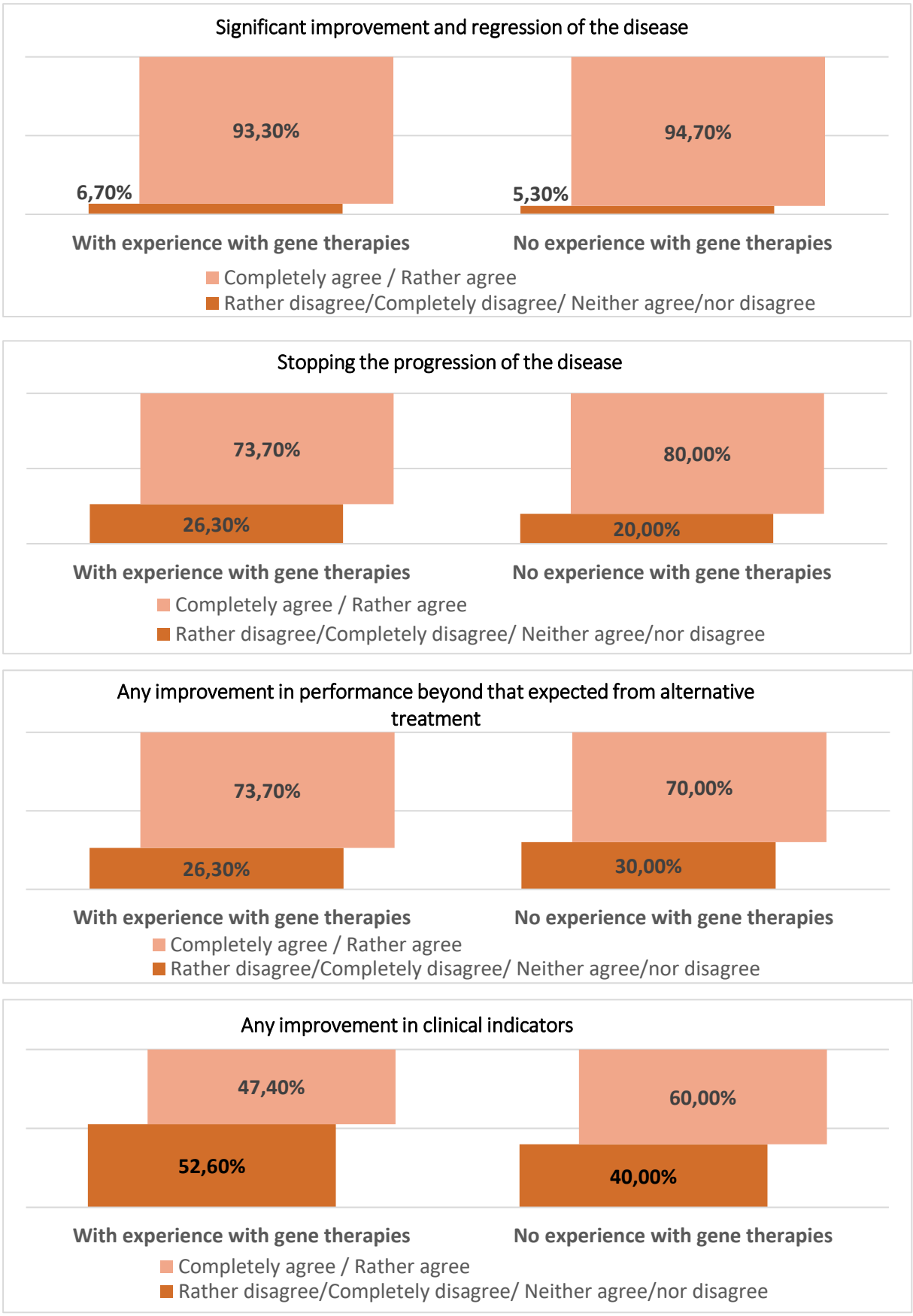

Fig. 16. Distribution of the degree of agreement with the given hypotheses for the success of treatment with GTs in the presence of alternative treatment in the subgroups of medical specialists.

12. Minimum duration of therapeutic response after GT administration

For the purposes of the study, healthcare professionals were asked to freely determine the minimum period of time after stopping disease progression following the administration of GT, after which the treatment can be considered successful. The range of periods in months indicated by the respondents is quite wide – between 3 and 240 months, with the average value being 28.53 ± 40.53 months. Healthcare professionals without clinical experience with GTs indicated a necessary duration of 31.56 ± 49.52 months, while the remaining professionals surveyed expected an average of 24 ± 21.56 months. No statistically significant difference between the subgroups was observed (p=0.61).

13. Optimal period of time and frequency of follow-up of treated patients

The many limitations in the preliminary clinical trials of GTs are the main reason for the limited data on efficacy and safety of the products. The opinions of the medical professionals participating in the study regarding the follow-up of patients have quite wide time limits. Of all respondents, 71.4% (n=35) entered a specific value in years for follow-up after GT administration, with the minimum freely specified value being 1 year and the maximum - 20 years. The mean value for the duration of patient follow-up among the respondents was 7.94 ± 5.81 years. The remaining part of the respondents indicated lifelong follow-up of patients (n=14; 28,57 %), with a notable similarity of opinion in the subgroups (p=0,48) (Table 6).

Table 6. Distribution of medical specialists according to their stated long-term follow-up period (n = 49).

Long-term follow-up period	Clinical experience with GTs	Number of respondents	Percentage of the separate group
Fixed follow-up period (n=35)	Yes	13	68.42%
	No	22	73.33%
Lifelong follow-up (n = 14)	Yes	6	31.58%
	No	8	26.67%

The usual regulated period in the EU for monitoring patients treated with GTs is between 12 and 180 months, depending on the product and the specific requirements of the EMA. The significant proportion of respondents

preferring lifelong follow-up of patients (n=14; 28.6%) indicates that perhaps the upper limit of 15 years of follow-up is small and it is necessary to consider an option for longer-term additional follow-up at the national level as a domestic health policy.

Regarding the frequency of follow-up, the surveyed medical professionals are united around the proposed option of follow-up every three months (n=26; 53.1%), with half as many respondents preferring monthly monitoring (n=12; 24.5%). Support for six-month follow-up (n=8; 16.3%), a period familiar to specialists from mandatory protocols for some ongoing treatments, is relatively low. The option to follow up patients only once a year received the least support (n=3; 6.1%).

Despite the lack of a statistically significant difference (p= 0.13), a much more distinct preference is observed in the responses of specialists with clinical experience with GTs, which is absent among the responses of specialists without experience with GTs (Fig. 17).

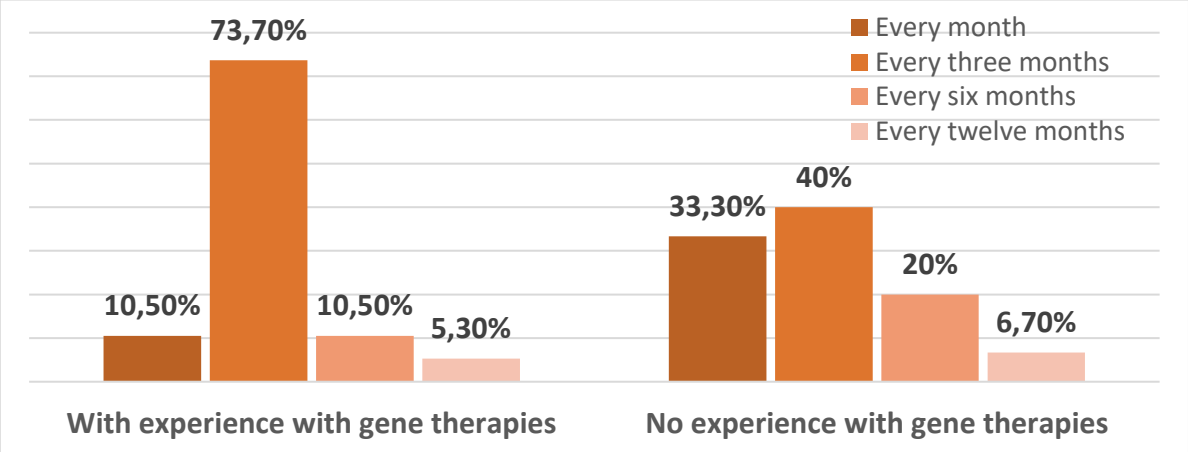

Fig. 17. Distribution of preferences for frequency of regular follow-up of patients who have undergone GT treatment in the subgroups of medical specialists.

14. Collection and analysis of data from long-term patient follow-up

Analyses of data from long-term follow-up of patients who have undergone treatments are of essential importance not only from a patient safety perspective, but they also serve to control reimbursement costs by providing a more complete picture of the real value and benefit of treatments in the long term.

Within Bulgaria, the collection and analysis of such information could be the prerogative of the Ministry of Health (MoH), the Bulgarian Drug Agency

(BDA), the National Health Insurance Fund (NHIF), as well as the Expert Councils on Medical Specialties under the Minister of Health. Among these options, the surveyed medical specialists most often expressed a preference for the MoH (n=34; 70.8%) (Fig. 18).

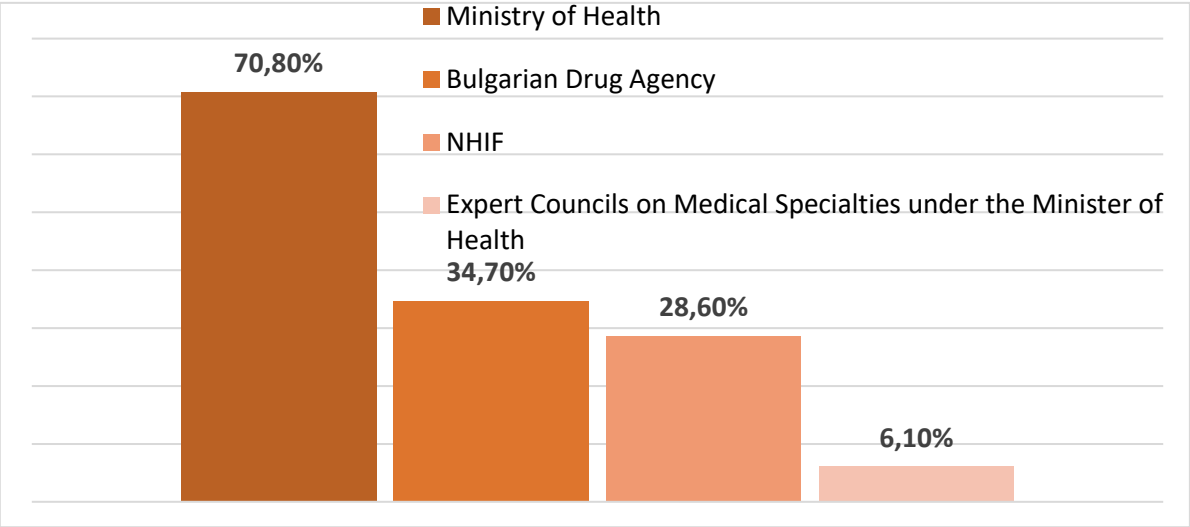

Fig. 18. Distribution of preferences for a health institution in Bulgaria suitable for collecting data from the long-term follow-up of the GT effectiveness.

The high support for the Ministry of Health as an institution for collecting and analyzing patient data is perhaps an appropriate choice, as it is an institution independent from the NHIF and thus the financing processes will be separated from the monitoring of the effectiveness of the treatments. This will allow for better control over the implementing institutions and greater transparency of the current procedures.

II. Study of patients' opinions and attitudes regarding the conditions for access to GT treatment in Bulgaria

1. Socio-demographic data about the participants

16 were parents of pediatric patients (with parents also completing sociodemographic information about their children). From the adult patients, 7 fully completed questionnaires were received and 1 questionnaire with missing data for one of the open-ended questions, which was therefore not excluded from the study. From the second type of questionnaire for relatives of pediatric patients, 16 fully completed questionnaires were collected. Among them, there were no incorrectly completed questionnaires.

The mean age of the parents was 42.44 ± 9.55 years, while that of the patients was 19.25 ± 15.33 years. The age of the patients with hemophilia ranged from 2 to 60 years. All patients in the study were male, with a predominance of women among the parents – 81.25%.

The mean age at diagnosis was 2.33 ± 3.42 years. The majority of the patients in the study have hemophilia type A (n=23; 95.8%) and only one patient has hemophilia type B. More than half of the respondents defined their disease as severe (n=16; 66.7%).

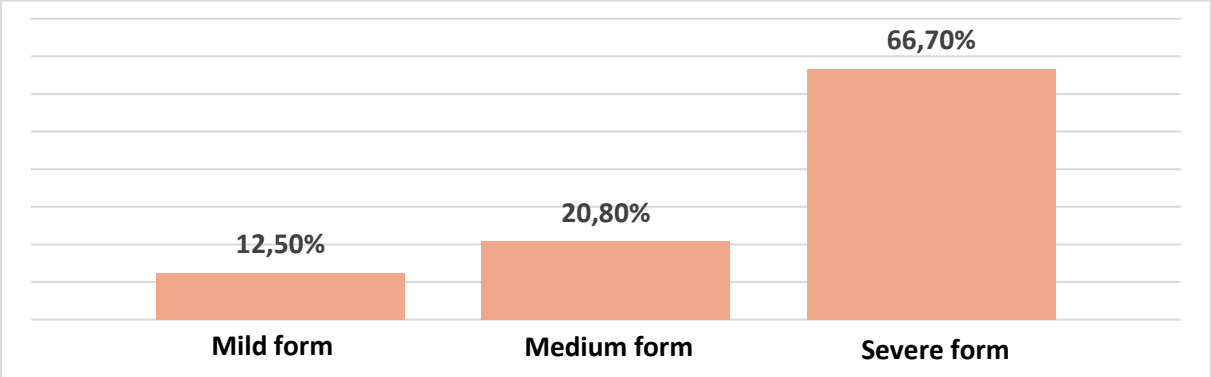

Fig. 19. Distribution of disease severity among participating patients at the time of the study (incl. pediatric patients).

The majority of the patients receive the current standard treatment for the disease (prophylaxis) (n=20; 83.3%), with the remaining patients in the study receiving treatment as needed or in the event of bleeding (n=4; 16.7%). There were no patients in intensive care participating in the study.

A majority of the patients in the study reported bleeding at least once a month or once every three months (n=18; 75%) (Fig. 20).

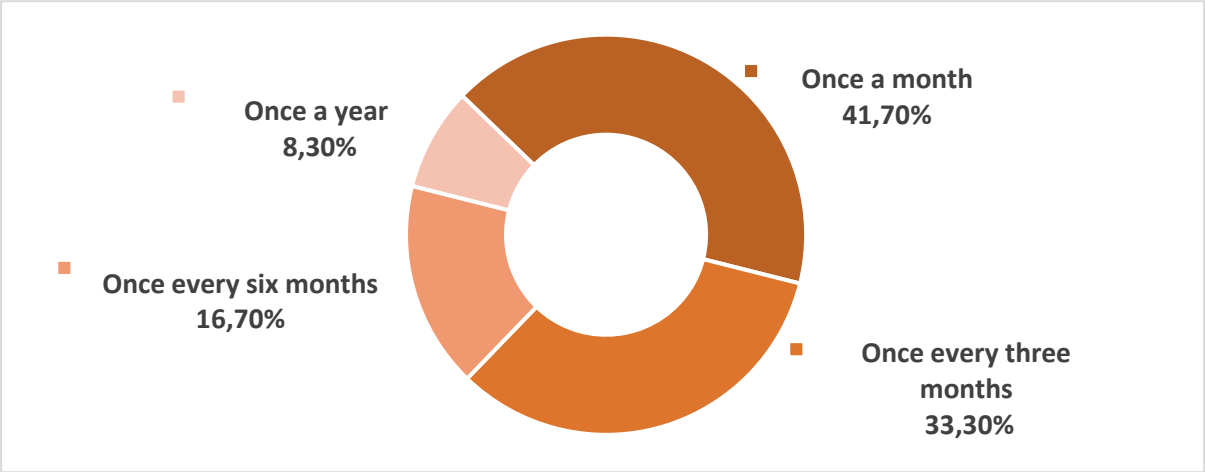

Fig. 20. Incidence of bleeding episodes among participating patients (incl. pediatric patients).

Over half of the patients participating in the study had joint disorders as a result of the disease (n=14; 58.3%), with a quarter of all respondents describing their joint disorder as mild in their daily lives.

A larger proportion of patients in the study had no complications identified as a result of the current treatment (n=16; 66.7%), but given the age distribution of the participating patients and the predominant pediatric patients (n=16; 66.7%), it can be said that the rate of complications among patients in the general population is likely to be significantly higher.

Evaluating treatment outcomes from the patients' perspective is important both for their subjective personal assessment of their quality of life, but also for seeking alternative treatments, if any. In the study, the largest share of respondents assessed the results of the treatment as very good so far (n=14; 58.3%), and the smallest number of respondents gave a poor assessment of the treatment (n=4; 16.7%) (Fig. 21).

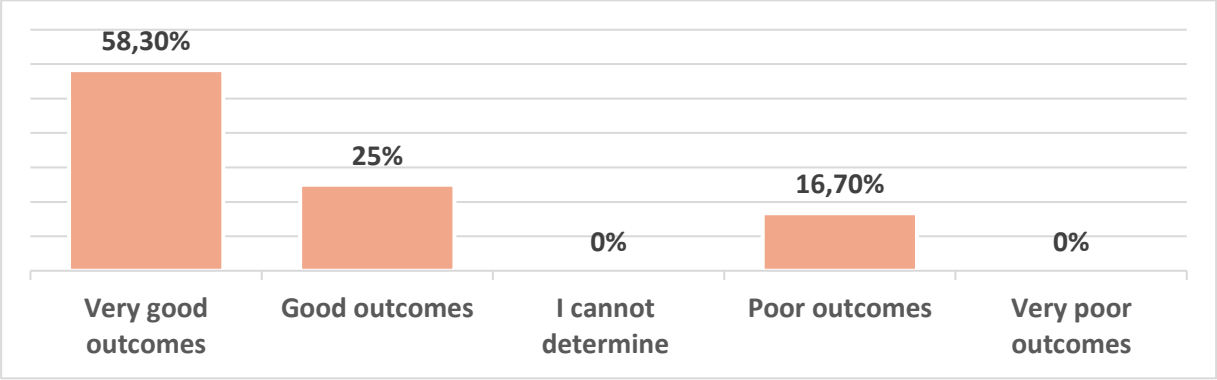

Fig. 21. Distribution of assessments for the results of the current treatment.

The lack of "very poor treatment outcomes" assessments is a good indicator of the level of satisfaction with the current organization of treatment of hemophilia patients in Bulgaria.

Despite the prevailing positive assessments of the treatment outcomes, more than half of the respondents stated that they would change it if they had the opportunity (n=13; 54.2%). As reasons for the desire to change treatment, most respondents cited common problems in disease prophylaxis – insufficient blood clotting factor levels, rapid decrease in factor levels in the periods between prophylaxis, or the method of administration for pediatric patients.

2. Awareness of GT treatment options for patients

More than half of the participants in the surveys aimed at patients and parents stated that they were aware of the possibilities for GT treatment (n=16; 66.7%), citing patient organizations as the main source of information (n=10; 62.5 %). The second most frequently cited source of information is medical professionals (n=9; 56.25%). Significantly fewer respondents mentioned the Internet (n=5; 31.25%) or pharmaceutical companies (n=1; 6,25%).

Although it is beyond the scope of the study to determine the specific level of awareness of GTs among patients, there are interesting results which show that respondents who would not change anything in their current treatment are distinguished by a higher rate of awareness about the possibility of GT treatment (n=9; 81.8% of the subgroup). Although there is no statistical difference in the subgroups with and without a desire to change

treatment (p=0.21), the results may be due to uncertainty about the effectiveness and safety of GT treatment.

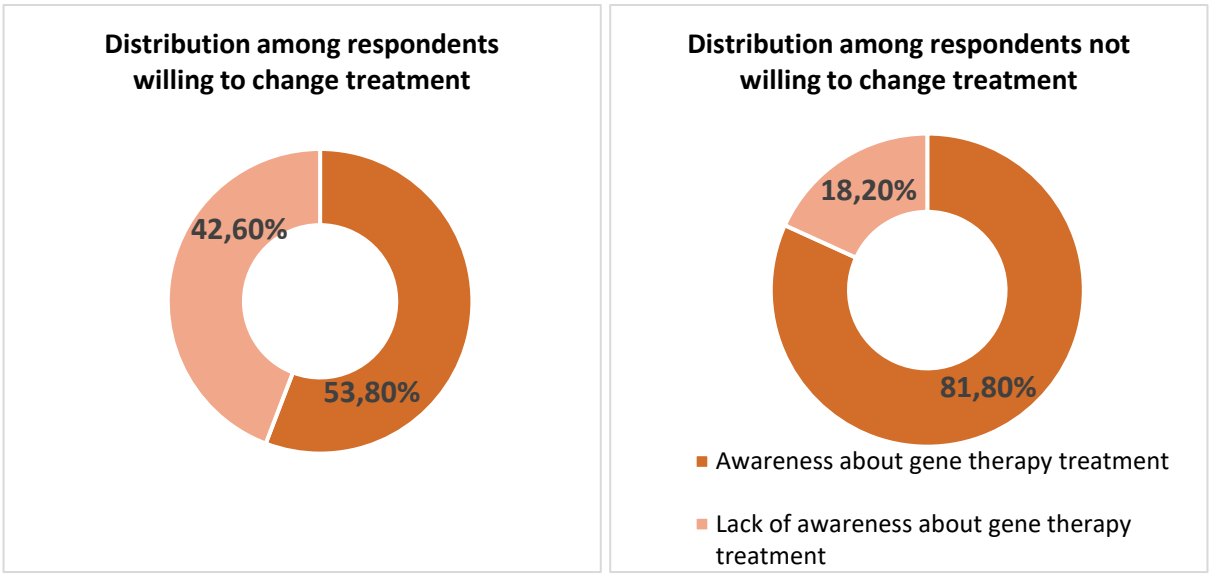

Fig. 22. Distribution of respondents' awareness according to their willingness to change current treatment.

The distribution of awareness is different when comparing the subgroups of adult patients and the parents of pediatric patients, respectively. Over half of the participants in the subgroups thus formed are informed about the possibilities for treatment with GTs (n=6; 75% of patients; n=10; 62.5% of parents), with no statistical difference found between them (p = 0.67).

3. Opportunities for access to GT treatment in Bulgaria

Despite the relatively good awareness of the respondents, a small number of them have discussed the possibility of accessing GT treatment with their treating physician (n=6; 25%). This result is most likely related to the fact that there are currently no mechanisms for public funding of GT treatments outside of Ordinance No. 2 of March 27, 2019 and Ordinance No. 10 of November 17, 2011. This is confirmed by the responses received, with access most often discussed only under the condition of full funding from the NHIF. It is notable that a rather small share of the respondents from the subgroup of adult patients have discussed GT treatment at all (n=1; 12.5%), in contrast to the same share among parents of pediatric patients (n=5; 31.2%).

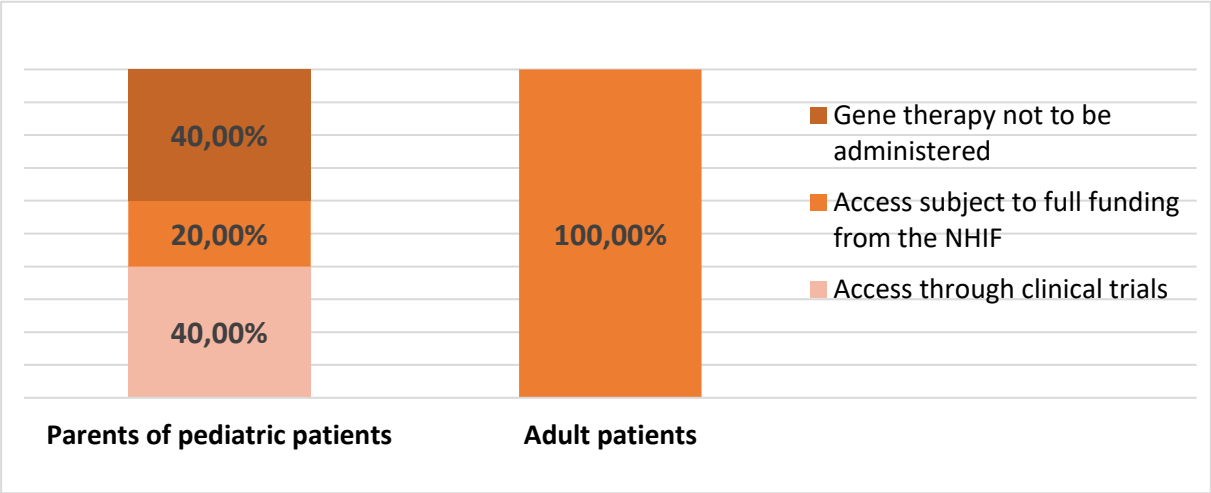

Fig. 23. Distribution of respondents according to the options for accessing GT treatment discussed with a medical professional.

The freely given reasons for not administering the treatment were insufficient clinical experience with children, lack of funding and uncertainty of the outcomes. There was no statistically significant difference between the two subgroups of respondents (p=0.63).

4. Establishing a minimum required threshold of treatment success for public funding

With set minimum success thresholds for hypothetical GT in the range of 50% - 80%, the surveyed patients and parents of pediatric patients most often choose to finance treatment with an effectiveness of over 80% (n=9;37.5%) (Fig. 24).

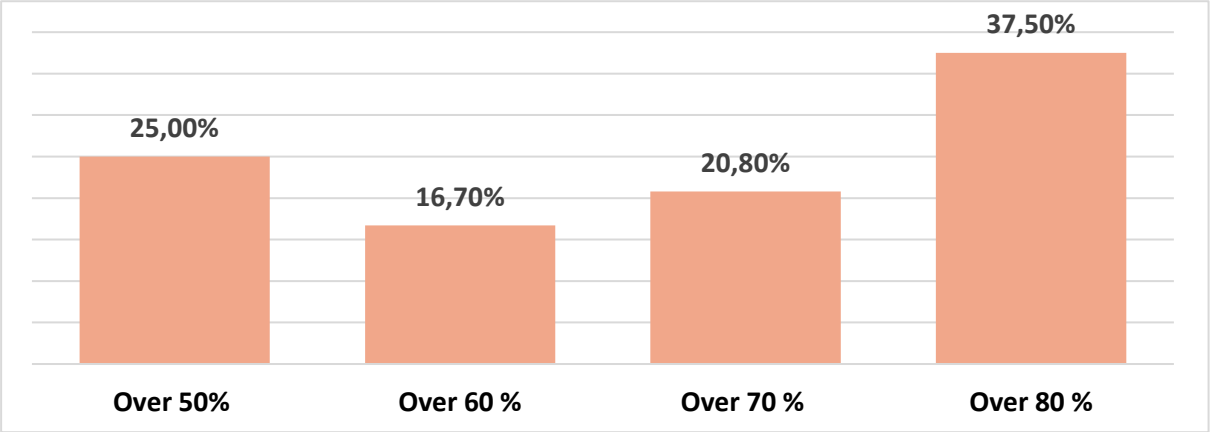

Fig. 24. Minimum success thresholds for GTs for public funding.

The results obtained from the patients are closer to the opinion of the medical specialists without experience with GTs (Table 1 and Fig. 4).

5. Assessment of the attitude towards GT treatment in the context of insufficient information on long-term clinical safety and effectiveness

The definitions of “willingness” and “readiness” for GT treatment used in this study refer to respondents who would be willing to undergo GT treatment if its effectiveness were proven. Slightly less than half of the patients and parents surveyed stated that they would accept GT treatment in the absence of sufficient information on the long-term safety and effectiveness of the product if there was data on the impact on quality of life and survival (n=11; 45.8 %). There was no statistical difference between the two separate subgroups of respondents (p = 1.00), with a slightly higher willingness to treat being observed in adult patients compared to the subgroup of parents of pediatric patients (Fig. 25).

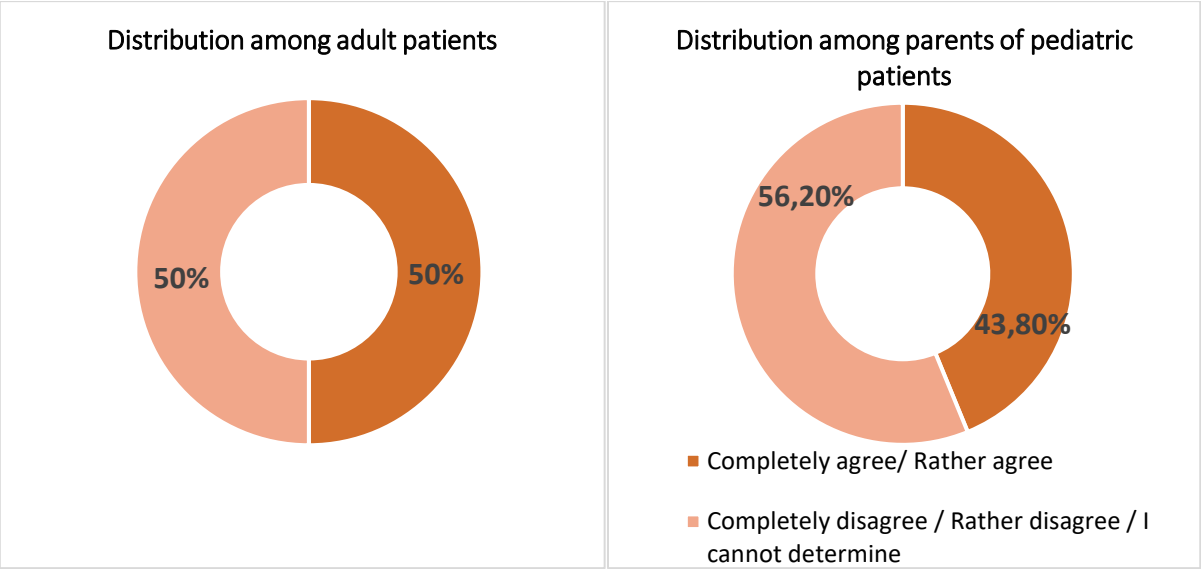

Fig. 25. Distribution of attitudes towards GT treatment.

No statistically significant difference in readiness for treatment was observed between the opinions of the respondents divided into subgroups depending on their level of awareness (p = 1.00), and a difference of 7.2% was found in the share distribution of the attitude in the subgroups. The obtained results reveal an inverse relationship between awareness and readiness for treatment. Assuming an average level of awareness for the respondents who declared such readiness, probable reasons for this may be the small volume of data from clinical studies and follow-ups.

6. Financing GT treatments with public funds

Reimbursement of GT treatments is clearly supported by the majority of the respondents in the study. Three-quarters of the respondents agree with funding GT regardless of the current safety and efficacy data (n = 18; 75%), and the high support observed is not influenced by either the level of patient awareness or their desire to change treatment (Fig. 26 and Fig. 27).

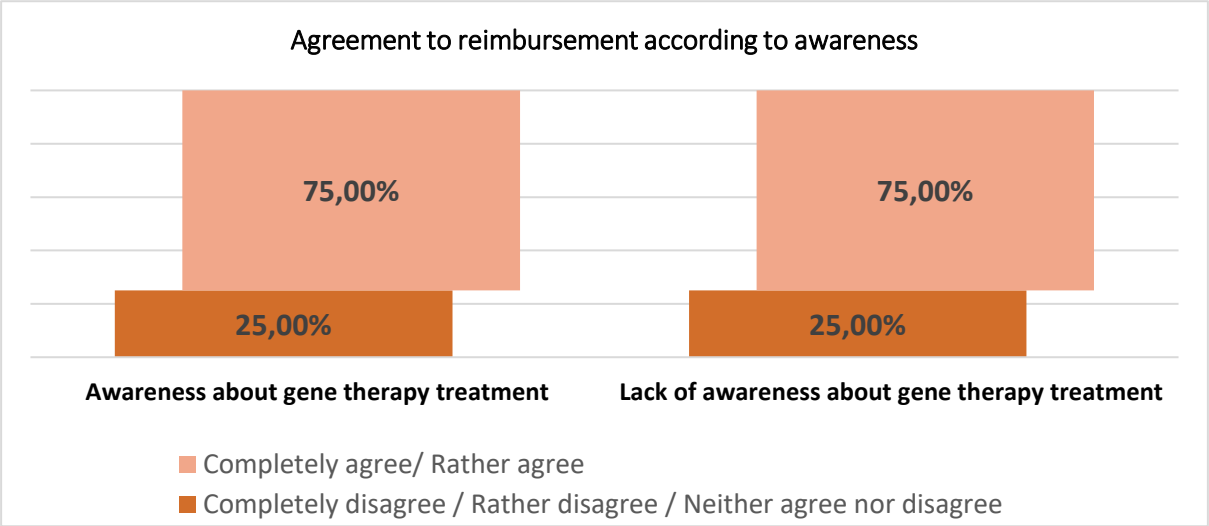

Fig. 26. Distribution of the degree of agreement to reimbursement of GT treatments according to the awareness of the respondents.

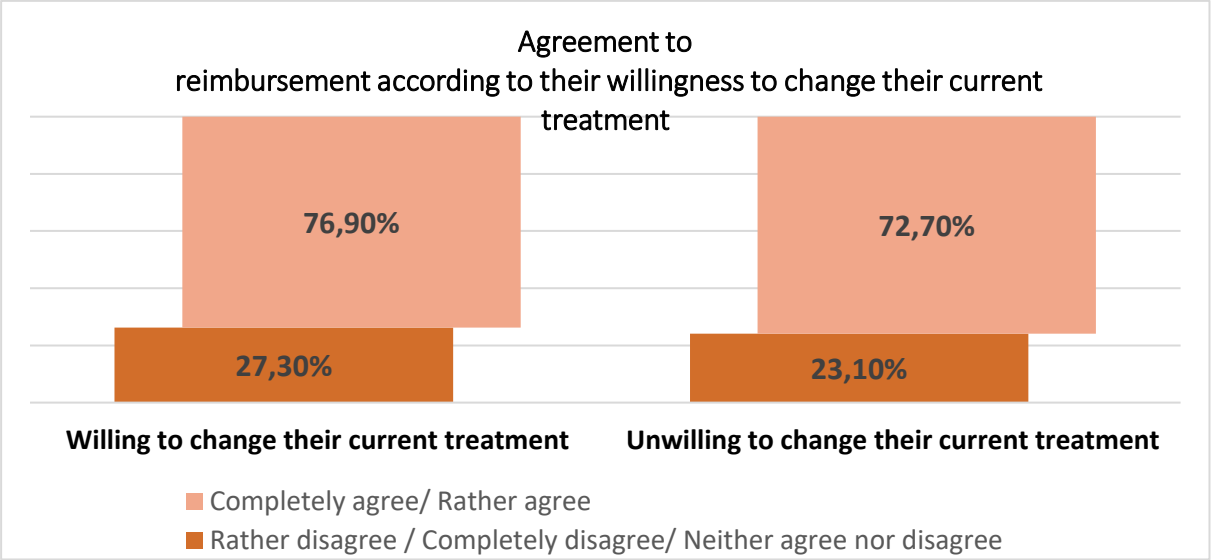

Fig. 27. Distribution of the degree of agreement to reimbursement of GT treatments according to the willingness to change the current treatment of the respondents.

The high support for public funding, regardless of the desire to change current treatment and their awareness, is most likely an expression of the respondents' natural desire for greater choice in the treatment of the chronic disease.

Predictably, the attitude towards GT treatments is decisive for the support of their reimbursement, as the difference between the two

subgroups in the level of agreement for public financing according to "willingness" is nearly 30% (p = 0.17). It can be said that as patients' willingness to undergo GT treatment increases, support for reimbursement of therapies will also increase.

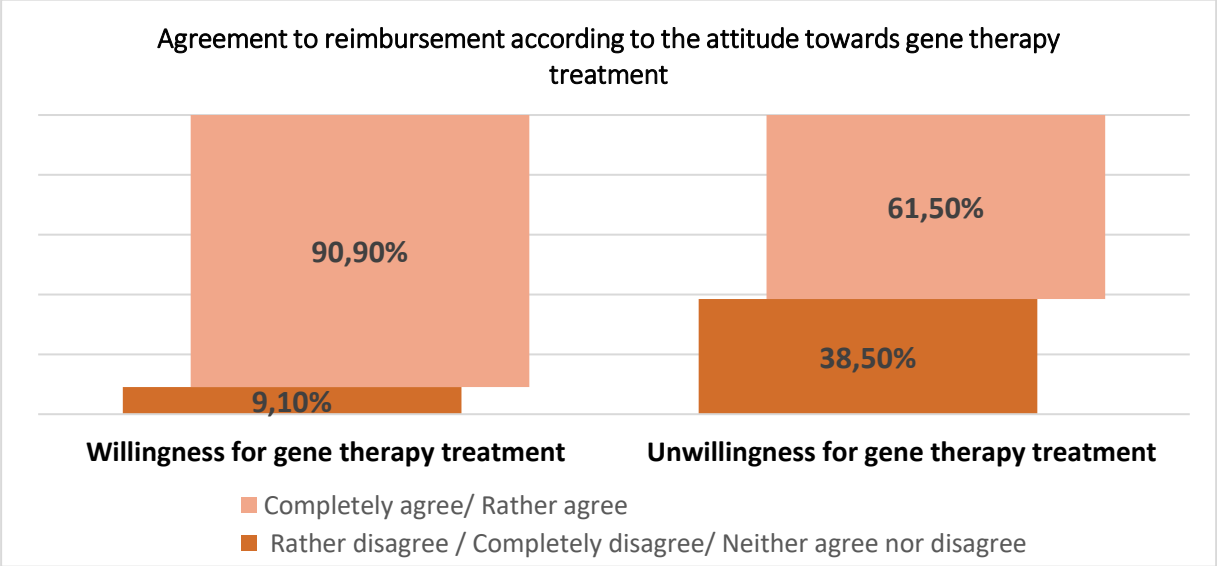

Fig. 28. Distribution of the degree of agreement to reimbursement of GT treatments according to the attitude of the respondents.

7. Establishing an appropriate method of reimbursement for GTs in Bulgaria

The participants in the study among patients and parents were introduced in several consecutive questions to the three reimbursement methods, identical to those used in the study among medical professionals – periodic payment through installments upon reaching and maintaining a certain clinical outcome (1), periodic payment through installments until the occurrence of an adverse event linked to the use of the product (2), and one-time full payment for the treatment product after use (3).

The option of payment through periodic installments linked to the achievement and maintenance of a certain clinical outcome was considered an appropriate financing method according to 33.3% of the surveyed adult patients and parents (n = 8) (Fig. 29).

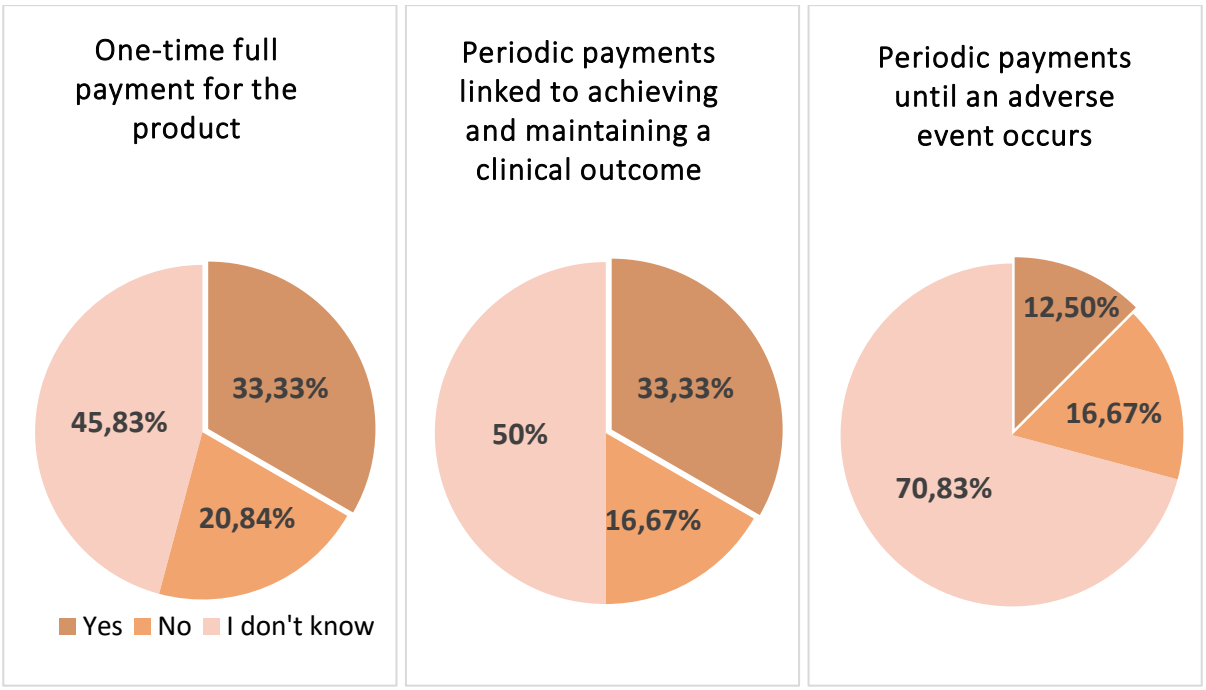

Fig . 29. Distribution of support for the proposed methods for reimbursement of GTs.

A significant number of the respondents noted that they did not know whether the methods were suitable for application in Bulgaria, which means that most likely the method of financing the treatments does not really matter to them, but rather the availability of access to them. The opinions of adult patients and parents of pediatric patients regarding the methods of financing do not differ significantly, although the share of support in the subgroups varies.

When directly comparing the three public funding options with only one of them selected as the most appropriate, the respondents in the study are almost equally divided between periodic payments linked to achieving and maintaining a clinical outcome (n = 12; 50%) and full payment for therapy (n = 10; 41.7%). There is little support for funding through periodic payments linked to patient safety (n = 2; 8.3%).

From the perspective of patients and parents, the effectiveness of treatments is a top priority and benefit. The safety of GTs is an important aspect that becomes perhaps secondary if the therapies actually work and lead to improved quality of life.

8. Reimbursement of GT costs in case of lack of treatment effectiveness

Both among medical professionals and among the surveyed adult patients and parents of pediatric patients, the prevailing opinion is that the costs of unsuccessful treatment should be reimbursed by the pharmaceutical manufacturer. The agreement among patients and parents is higher than that of specialists – 75% of them support the return of funds (n = 18) compared to 57.1% (n = 28) of specialists. The observed difference is logical given the different perspectives of the respondents.

Although there was no statistically significant difference in opinion between the subgroups of parents and adult patients (p = 0.13), a higher prevailing share of agreement was found in the subgroup of parents (n = 14; 87.5 %). Among adult patients, the opinion on reimbursement by the pharmaceutical company was equally divided (agreement of n=4; 50%). The respondents' awareness and attitudes towards GTs did not influence their opinion on reimbursement.

Most medical professionals, as well as the majority of the patients and parents participating in the study, express agreement both on public funding and on the return of funds in case of treatment failure. Factors influencing the level of support in the respondent subgroups (e.g., specialists' experience with GTs, willingness to change current treatment, attitudes towards GT of patients/parents, etc.) do not have a significant impact on the general opinion and apparent agreement regarding the provision of real access to this type of treatment, which remains high among those participating in the study.

9. Expectations regarding administration and outcomes of GTs

It is a known fact that patients are not looking for specific treatment, but health, the definition of which is complex and depends on numerous factors, implying a certain subjectivity. Given the specificity of the congenital chronic disease, for the purposes of the study, the expectations of the patients and parents were reduced to achieving and/or maintaining specific health outcomes that are an easily recognizable part of their life with hemophilia.

9.1. Minimum period of time without bleeding episodes as an indicator of treatment success

The patients and parents surveyed had to determine the minimum period of time without bleeding episodes after which they would consider the treatment with GT to be successful. The patients' choice was reduced to five options, from one to five or more years. According to the results obtained, the respondents would most often consider the successful GT to be one that stops spontaneous bleeding for 3.54 ± 1.69 years. The expectations of adult patients (3.75 ± 1.83 years) were higher compared to the expectations of parents of pediatric patients (3.44 ± 1.67 years). No statistical difference was observed between the subgroups (p = 0.57).

9.2. Minimum period of time of stopping replacement therapy and maintaining stable blood clotting factor levels as an indicator of treatment success

Replacement therapy for clotting factor deficiency is the main prophylactic treatment for hemophilia. Therefore, as a kind of measure of the success of GT treatment, the surveyed patients and parents indicated the optimal period of time after GT administration, within which a stable level of clotting factor would be maintained and the need for replacement therapy would be eliminated. The proposed options were five, with a minimum period of one year and a maximum of five and over five years. The mean value obtained was 3.17 ± 1.74 years. There was no statistical difference between the answers for the period of time indicated by the respondents from the different subgroups of the sample (Table 7).

Table 7. Minimum expected period of time with maintenance of stable blood clotting factor levels and elimination of the need for replacement therapy in the subgroups of respondents (n = 24).

Subgroup of respondents	Number (n)	Mean value of minimum time period (years)	Standard deviation (years)	P - value
Adult patients	8	3.25	1.98	0.88
Parents of pediatric patients	16	3.13	1.67	
Willing to change treatment	13	3.38	1.90	0.52
Unwilling to change treatment	11	2.91	1.58	
Awareness about GT	16	2.81	1.72	0.87

Subgroup of respondents	Number (n)	Mean value of minimum time period (years)	Standard deviation (years)	P - value
Lack of awareness about GT	8	3.88	1.64	
Willingness for GT treatment	11	2.45	1.51	0.36
Unwillingness for GT treatment	13	3.77	1.74	

The shortest preferred time periods for maintaining the level of blood clotting factor without the need for replacement therapy were indicated by respondents who expressed willingness for treatment with GT (2.45 ± 1.51) and those informed about GT (2.81±1.72 years).

9.3. Minimum reduction in bleeding episodes over one year as an indicator of treatment success

The last question of the survey for adult patients and parents of pediatric patients concerned the minimum percentage by which the number of bleeds should be reduced on an annual basis, which, in their opinion, would be an indicator of success of GT treatment. Considering the lack of response from one respondent, the mean value obtained for the entire sample is a decrease of 44.43% ± 39.28% (n = 23). The distribution of the indicated values by subgroups differs significantly (p = 0.04), with patients indicating much higher values (65.71% ± 40.25%) compared to parents of pediatric patients (35.13% ± 36.21). This could be due to the higher emotional and social burden of the disease that parents of children with hemophilia have, and which affects the results so that any improvement is significant (Table 8).

Table 8. Minimum expected reduction in bleeding episodes on an annual basis in the respondent subgroups (n = 23).

Subgroup of respondents	Number (n)	Mean minimum decrease (percentage)	Standard deviation (percentage)	P - value
Adult patients	7	65.71	40.25	0.04
Parents of pediatric patients	16	35.13	36.21	
Willing to change treatment	12	40.42	41.80	0.50
Unwilling to change treatment	11	48.82	37.83	
Awareness about GT	15	49.47	38.96	0.96
Lack of awareness about GT	8	35.00	40.71	
Willingness for GT treatment	11	48.36	37.32	0.43
Unwillingness for GT treatment	12	40.83	42.31	

It is notable that adult patients with hemophilia have generally higher expectations for the use of GTs compared to parents of pediatric patients in terms of the studied parameters of treatment success.

III. Example model for reimbursement of GTs in Bulgaria

Based on the data obtained and summarized from the two surveys among stakeholders in access to GT treatment - medical experts, adult patients and parents of pediatric patients, a model for public funding and, respectively, ensuring patient access to GT treatments was derived. The model is based on the currently applicable regulations in the EU and Bulgaria regarding market authorization and reimbursement of new ATMPs.

1. Centralized marketing authorization of a new product for GT

Based on the centralized decision for the marketing of a new medicinal product under Regulation (EC) No. 1394/2007 and Regulation (EC) No. 726/2004, the authorisation issued by the EMA is valid for all Member States and countries of the European Economic Area. This eliminates the need for the pharmaceutical company – holder of the authorisation or its representative (if not established on the territory of Bulgaria) to submit a separate application for marketing authorisation for use in Bulgaria to the BDA.

2. Registering a price for the new treatment product

In addition to an application for price registration, the holder of the authorization may simultaneously submit ***an application for inclusion in the Positive Drug List*** (Article 7a of the Regulation on the conditions, rules and procedure for regulating and registering the prices of medicinal products), which is in turn a mandatory condition for public funding of treatments. According to Articles 30a and 37 of the same Regulation, the National Council on Prices and Reimbursement of Medicinal Products must prepare ***a health technology assessment*** and issue an opinion within 180 days, after which the holder of the marketing authorization must ***negotiate centrally with the NHIF conditions for financing*** and delivery of products through a contract with fixed discounts from the maximum registered price of the medicinal and medical products.

3. Funding algorithm

According to the results of the presented study, the most suitable option according to medical specialists, and at the same time optimal from an economic point of view, would be a ***periodic payment option until the full cost of the treatments is recovered with fixed parameters***.

- ✓ **Terms and conditions for periodic payments.**

Maintaining or achieving ***a specific clinical outcome*** is a common option that has been used successfully in other Member States for single-dose treatments.

- ✓ **Monitoring and assessing the therapeutic outcomes of GT administration.**

The National Council on Prices and Reimbursement of Medicinal Products may order monitoring of the therapeutic effects of publicly funded treatments for 1 to 3 years for the purpose of "analyzing the effective and appropriate spending of public funds on a medicinal product." Given the extremely high cost of GTs, as well as the uncertainty of their application, monitoring of therapeutic outcomes should be financially linked to payments for the treatment, which is confirmed by the opinion of the experts who participated in the study.

✓ **Period of assessment of the therapeutic effectiveness of treatments.**

The National Council on Prices and Reimbursement of Medicinal Products may order monitoring of the therapeutic effects of publicly funded treatments for 1 to 3 years for the purpose of "analyzing the effective and appropriate spending of public funds on a medicinal product." Given the extremely high cost of GTs, as well as the uncertainty of their application, monitoring of therapeutic outcomes should be financially linked to payments for the treatment, which is confirmed by the opinion of the experts who participated in the study.

✓ **Frequency of data collection to assess the therapeutic effectiveness of treatments on selected indicators.**

A quarterly follow-up for the first 24 months after the administration of GT could be an optimal option, which was agreed upon by 53.10% of the experts surveyed. With satisfactory clinical outcomes, the agreed periodic payment for the treatments is paid.

✓ **Reimbursement of costs in case of unsuccessful treatment.**

Given the high level of agreement observed in both groups of respondents, it can be said that part of the funding conditions should also include reimbursement of treatment costs in the event of therapeutic failure.

If failure is established, within the first year after administration the funds invested in the treatment to date are returned by the pharmaceutical manufacturer/its representative in the country. This guarantees reimbursement of costs in the event of ineffective treatment. In the event that a deterioration in the patient's condition is established below the effectiveness threshold specified in the contract with the NHIF ***after the twelfth month following administration***, suspension of payments for the treatment is a reasonable option. In this way, the funds for treatment are spent more appropriately - they are paid while the therapy is actually working until the 24th month following administration, addressing the fact that the treatment has had its proven clinical benefit for patients within the first year. Full reimbursement of funds by the manufacturers of GTs after this period would most likely be unacceptable and unjustified as well.

4. Long-term follow-up of patients.

✓ **Institution for collecting and analyzing data from long-term post-therapeutic follow-up.**

According to the majority of medical professionals surveyed (70.8%), the Ministry of Health is the appropriate institution for collecting and analyzing data from long-term patient follow-up**.**

✓ **Frequency of data collection for long-term follow-up.**

Given the currently effective six-monthly protocols for continuing treatment of hemophilia patients, among whom the study was conducted, the option of follow-up examinations **every six months after the end of the second year** following therapy administration will not significantly increase the healthcare budget.

✓ **Duration of long-term follow-up.**

Due to the very specificity and action of GTs as medicinal products, as well as the currently valid protocols for ongoing treatment of chronically ill patients, the presented algorithm offers **lifelong monitoring of patients**, a preferred option by a significant proportion of the participating specialists (28.6 %). In the long term, this option is perhaps the most reliable and appropriate for all stakeholders in GT treatment – patients, medical specialists and health authorities.

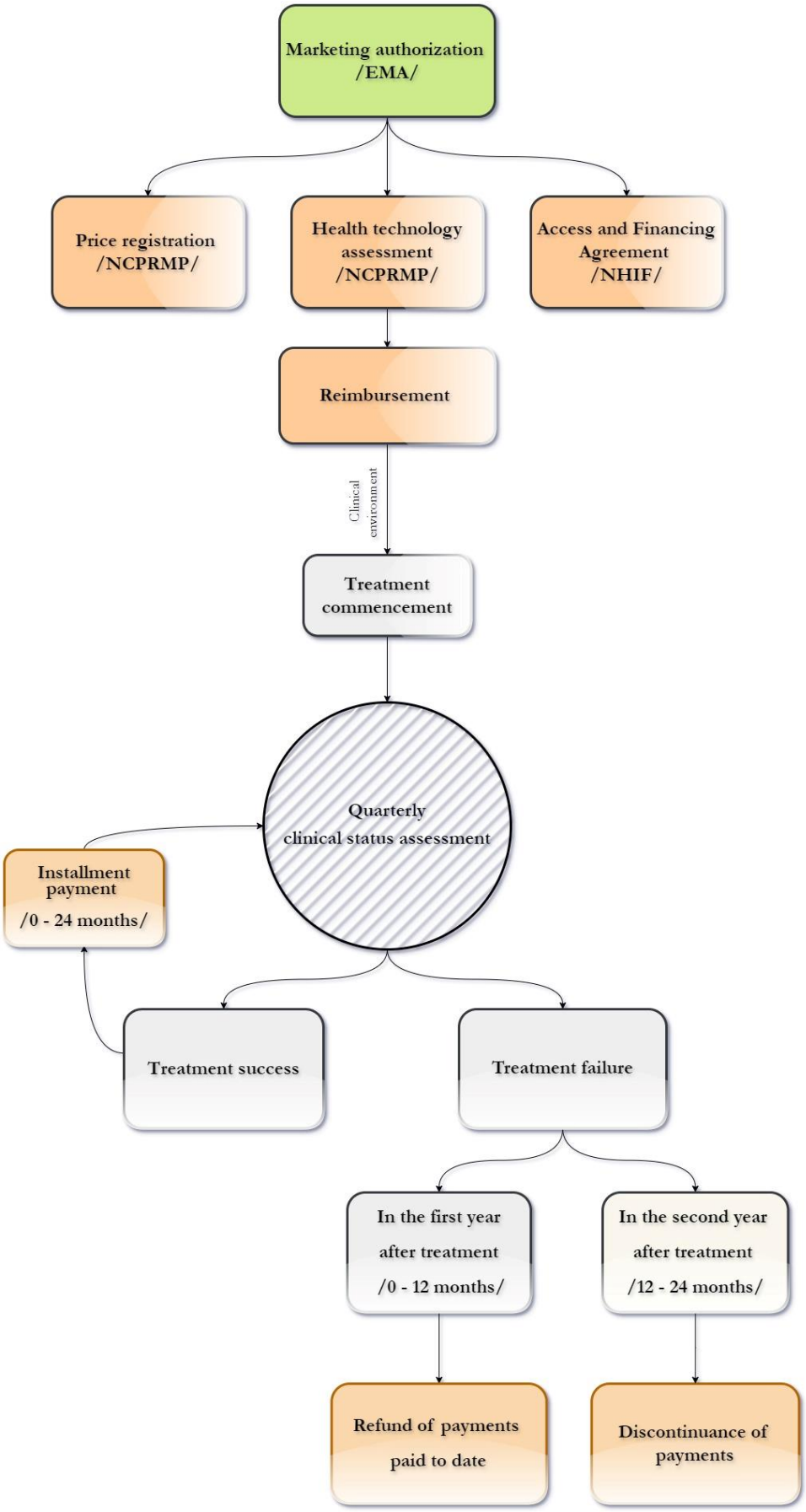

Fig. 30. Example model for reimbursement of GTs in Bulgaria.

CONCLUSIONS

1. Medical specialists' clinical experience with GTs is a factor that influences the attitudes towards administration of the therapies and influences the expected threshold of minimal effectiveness as an indicator of treatment success. Certainty in the treatment outcomes is a significant element shaping the attitudes of specialists in the absence of clinical experience with GTs.

2. The lack of alternative treatment for patients, as well as the importance of financing treatments for pediatric patients, regardless of the availability of alternative therapy, are factors of great weight among medical professionals regarding the priority reimbursement of different treatments.

3. Based on the opinions of the medical professionals participating in the study, survival rate as an independent factor for reimbursement priority has a higher weight compared to improving quality of life.

4. Medical professionals, regardless of their clinical experience with GTs, unanimously expect a sustained therapeutic response to GT treatments within several years after administration (28.53 ± 40.53 months).

5. Medical professionals support long-term follow-up of patients after GT administration for an average of 7.94 ± 5.81 years, with just under a third of them supporting lifelong follow-up (28.6%).

6. Despite the high assessment of the outcomes of their current treatment, over half of the surveyed adult patients and parents of pediatric patients with hemophilia express willingness to change treatment if there is a possible alternative.

7. The majority of the surveyed patients and parents of pediatric patients are informed about the possibility of GT treatment, with their main source of information being patient organizations.

8. Public funding and evidence of effectiveness are key to patients' attitudes towards GT treatment. Almost half of the patients and parents surveyed would agree to a proven effective GT treatment (45.8%) under condition of full public funding, even in the absence of sufficient data on long-term efficacy and safety.

9. The values obtained for the necessary minimum threshold of effectiveness for justified reimbursement of therapies among the surveyed patients and parents are high. For patients, the certainty of the therapeutic response and the outcome of the therapies are criteria of considerable importance.

10. The majority of healthcare professionals, patients and parents surveyed believe that public funding for GTs is justified and necessary. The result reflects a desire for more accessible therapeutic alternatives, regardless of the respondents' attitudes towards GT treatments.

11. The majority of respondents participating in the survey believe that the pharmaceutical manufacturer should reimburse the costs of treatment in the event of proven therapeutic failure.

12. Patients and parents of pediatric patients participating in the study did not show a preference for a specific method of financing treatments, as long as their patient access was ensured.

RECOMMENDATIONS

1. To the Ministry of Health:

1.1. To develop policies to involve medical experts with clinical experience with GTs in developing the conditions and solutions for public funding of treatments with these products.

1.2. To conduct international cooperation and stimulate the exchange and training of medical personnel, in order to increase expertise in GT treatments at the national level.

1.3. To develop and administer a national archival system for long-term follow-up of patients who have undergone GT treatment. Patient information should be publicly accessible to specialists and stakeholders in accordance with the Personal Data Protection Act.

2. To the National Health Insurance Fund:

2.1. To develop and implement mechanisms for deferred payment with public funds through periodic installments with fixed parameters for a minimum of 24 months, which would redistribute the budgetary impact of single-dose treatments over time and depending on the achieved clinical outcome.

2.2. To take into account and negotiate additional conditions for the refund of the funds paid in case of lack of therapeutic response or unsatisfactory clinical outcomes within a pre-fixed minimum period of time after the single-dose treatment.

3. To medical professionals:

3.1. To actively inform themselves about the results of clinical trials and follow-up of patients treated with GTs, both through established scientific databases and through health institutions such as the EMA, which publishes the required efficacy and safety reports.

3.2. To participate in decisions on public funding of treatments, as well as in the assessment of health technologies such as GTs in Bulgaria.

4. To patient organizations:

4.1. To lobby for the inclusion of more medical experts with clinical experience with GTs in national policies and decisions on funding new treatments.

4.2. To encourage patients to become more aware of innovative treatments, as well as alternative ways of accessing such treatments.

5. To medical establishments and medical universities:

5.1. To train personnel and facilitate the exchange of personnel with experience with GT treatments in order to increase the local level of expertise.

5.2. To promote research and development in the field of GTs.

CONTRIBUTIONS

Contributions of a scientific and theoretical nature

- An analysis of the opinions of medical specialists in Bulgaria on the conditions of patient access and criteria for payment for GTs with public funds was conducted.
- An analysis of the opinions of adult patients and parents of pediatric patients in Bulgaria on the conditions of access and criteria for reimbursement of GT was conducted.

Contributions of a scientific and applied nature

- A theoretical model for possible public funding of GTs has been developed in accordance with the analysis of survey data and taking into account national reimbursement specificities and good international practices.
- Specific and practically oriented recommendations have been made to all stakeholders concerned with patient access to GTs – the Ministry of Health, the National Health Insurance Fund, medical specialists and patient organizations, medical establishments and medical universities.

LIST OF SCIENTIFIC PUBLICATIONS AND PARTICIPATIONS IN SCIENTIFIC FORUMS RELATED TO THE DISSERTATION

Scientific publications

1. Kostadinov K, Marinova Y, Dimitrov K, Hristova-Atanasova E, Iskrov G, Stefanov R. Navigating Gene Therapy Access: The Case of Bulgaria in the Context of the EU Regulatory Landscape. Healthcare [Internet]. 2024 Feb 11;12(4):458. Available from: https://doi.org/10.3390/healthcare12040458
2. Kostadinov K, Popova-Sotirova I, Marinova Y, Musurlieva N, Iskrov G, Stefanov R. Availability and Access to Orphan Drugs for Rare Cancers in Bulgaria: Analysis of Delays and Public Expenditures. Cancer [Internet]. 2024 Apr 12;16(8):1489. Available from: https://doi.org/10.3390/cancers16081489
3. Marinova Y, Hristova-Atanasova E. Models for reimbursement of gene therapies. Rare Diseases and Orphan Drugs [Internet]. 2024 Dec 16;15(3–4):20–4. Available from: https://doi.org/10.36865/2024.v15i3-4.206
4. Marinova Y, Kostadinov K, Dimitrov K, Hristova-Atanasova E, Iskrov G, Stefanov R. Regulatory framework for market authorization of GTs in the EU and the USA. Scientific papers of the Union of Scientists in Bulgaria-Plovdiv. Series G. Medicine, Pharmacy and Dentistry, 2024, vol. XXXI. pp.193-196.

Participation in scientific forums

1. Xth International Conference of Young Scientists, 20-23 June 2024 – Plovdiv. Regulatory Framework for Market Authorization of Gene Therapies in the EU and the USA. Oral presentation.
2. European Hemophilia Consortium Conference, 03-06 October 2024 – Sofia. Patient Perspective and Expectations in Gene Therapies. Oral presentation.