The Chronic Urticaria Registry (CURE): Rationale, Methods, and Initial Implementation

Karsten Weller[1], Ana Giménez-Arnau[2], Clive Grattan[3], Riccardo Asero[4], Pascale Mathelier-Fusade[5], Mojca Bizjak[6], Michael Hanna[7], Marcus Maurer[1]; on behalf of the CURE Investigators

[1]Dermatological Allergology; Charité Allergy Center; Department of Dermatology and Allergy; Charité University Hospital; Berlin, Germany

[2]Department of Dermatology; Hospital del Mar; Autonomous University of Barcelona; Barcelona, Spain

[3]St John's Institute of Dermatology; London, United Kingdom

[4]Outpatient Clinic of Allergology; San Carlo Hospital; Paderno Dugnano, Italy

[5]Department of Dermatology and Allergology; Tenon Hospital; Paris, France

[6]University Clinic of Respiratory and Allergic Diseases Golnik; Golnik, Slovenia

[7]Mercury Medical Research & Writing; New York, NY, USA

Corresponding Author:

PD Dr. med. Karsten Weller

Department of Dermatology and Allergy

Charité – Universitätsmedizin Berlin

Charitéplatz 1

D-10117 Berlin

Germany

Tel: +49-30-450-518043

Fax: +49-30-450-518972

E-mail: karsten.weller@charite.de

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Abstract

Background: Chronic urticaria (CU) is a common disease, characterized by the recurrent appearance of wheals, angioedema, or both for more than 6 weeks. Its underlying biology is not well understood, and many patients do not obtain sufficient relief from recommended treatments. Patient registries are rapidly growing as a form of research, because they can provide powerful, data-driven insights about the epidemiology of diseases, real-world effectiveness of treatments, rare patient types, safety monitoring, healthcare costs, and opportunities for quality improvement of healthcare delivery.

Objectives: The Chronic Urticaria Registry (CURE) has been designed to improve the scientific understanding, clinical treatment, and healthcare planning of chronic urticaria patients. This report describes the rationale, methods, and initial implementation of this registry.

Methods: CURE is an ongoing, prospective, international, multicenter, observational, voluntary registry of patients with CU. Participation in CURE is open to any physician treating CU patients, regardless of location, medical specialty, or type of practice setting. CURE aims to collect data on all CU patients, with no intentional selection or exclusion criteria. It collects baseline and follow-up data on the patient's demographics, history, symptoms, trigger and risk factors, therapies, and healthcare utilization.

Results: CURE is a landmark achievement of the global urticaria medical community. As of 26 February 2020, 39 centers around the world have joined the registry and 35 have entered baseline data on a total of 2946 patients. Publications of this data will be forthcoming soon.

Conclusions: CURE is eagerly seeking the participation of more physicians and the support of more governmental, charitable, and commercial sponsors from around the world. Here, in this paper, we invite other physicians to join this unique project to improve the lives of patients with CU.

Introduction

Chronic urticaria (CU) is a common disease, characterized by the recurrent appearance of wheals, angioedema, or both for more than 6 weeks.[1] A recent meta-analysis of 11 studies on over 86 million people reported that CU had a point prevalence of 7 persons per 1000 population.[2] CU has a substantial burden on the patients' quality of life.[1,3-10] In 2013, urticaria was the third most burdensome skin disease and accounted for 0.19% of the entire global burden of disease, as measured in disability-adjusted life years (DALYs).[11]

The causes of CU are only partially understood. The majority of patients are classified as having chronic spontaneous urticaria (CSU), because no definite trigger can be identified that causes an outbreak of symptoms, and because other suspected aggravating factors, such as diet or stress, remain vague. By contrast, about one-third of patients have chronic inducible urticaria (CIndU),[12] meaning that a specific and definite trigger of symptom outbreaks (such as cold, pressure, sweating, or scratching) can be identified and diagnostically verified, even though it remains unclear why. Many patients have both CSU and CIndU, but the frequency and patterns of co-occurrence remain unknown. Patients with CU may experience wheals but not angioedema, angioedema but no wheals, or both wheals and angioedema. Given the wide variety of possible triggers and symptom presentations, many types of patients are rarely seen at any one clinic, thus further hindering the medical community's understanding of them.

The underlying biological mechanisms of CU are also only partially understood. It is well established that the release of histamine and other inflammatory molecules by mast cells (and perhaps also basophils) is the immediate mechanism causing the wheals and angioedema of urticaria.[13] But it remains mysterious why CU patients' mast cells release histamine so often or so easily, why wheals and angioedema occur when and where they do in CSU, why CIndU patients have an urticarial overreaction to their triggers, and why some of the symptom outbreaks resolve soon while others are more persistent. IgE autoantibodies or IgG or IgM autoantibodies, appear to play a key role in many cases of CSU, yet several other chemical signaling factors may also be involved in priming mast cells for degranulation.[14-19] The wide variety of external triggers, symptom presentations, and treatment responses suggests that various underlying pathways are involved for different patients. Again, this heterogeneity and complexity has hindered scientific progress to understand the underlying biology of CU.

Treatment guidelines developed jointly by numerous professional medical societies state that the first-line treatment for CU should be a non-sedating second-generation antihistamine at the standard recommended dose.[1,20] Yet based on many clinical trials, it seems

that only about 33% of patients will achieve complete symptom control with this first-line treatment.[21] For the remaining majority of patients who do not, the international guidelines recommend increasing the dosage up to 4x as second-line therapy, then omalizumab or ciclosporin as third-line therapy, and then further options with sparse, low-quality evidence.[1,20] Although many clinical trials have provided a solid evidence base for these recommendations, much remains unknown about the actual effectiveness of treatment in routine settings, especially for rarer subtypes of CU, unusual symptom presentations, and patients refractory to guideline treatments.

The objective for founding the Chronic Urticaria Registry (CURE) is to improve the scientific medical knowledge about CU, in particular about its symptom patterns, comorbidities, trigger and risk factors, burden on patients, response to various treatments, and costs to the healthcare system. The purpose of this initial report from CURE is to explain the rationale for this registry, describe its methods, and report on its implementation to date.

Rationale for the Registry

A patient registry is "an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves one or more predetermined scientific, clinical, or policy purposes."[22] Patient registries have become increasingly common for a wide range of diseases during the past decade, because they are able to answer many kinds of important questions that cannot be addressed adequately by traditional clinical trials and other forms of research. Randomized controlled trials (RCTs) remain the best way to scientifically demonstrate how much treatment benefit can be attributed to a medication or other form of therapy. But for various reasons, the effectiveness of treatments in routine clinical settings is often quite different from the efficacy reported in RCTs, especially in types of patients that were not eligible to participate, such as children, the elderly, patients with substantial co-morbidities, etc. RCTs are also of no use in determining which kinds of quality improvement changes need to be made in routine treatment to achieve better patient outcomes, and they rarely make any evaluation of the costs to the healthcare system. Most importantly, even large RCTs on urticaria rarely involve more than a few hundred patients. For this reason, they are incapable of providing sufficient proof of safety, despite often making such claims.

Safety can only be proven by very large, comprehensive, long-term, Phase IV, registry-based research.[23,24]

Patient registries are deliberately designed to gather large amounts of data from routine settings – without attempting to alter the treatment in any way – in order to provide insights into what is really happening in the healthcare system with all the various kinds of patients. They can tell us how effective medications or other treatments are with various subtypes of patients in real-world settings. Registries can alert us to serious harms that might never be recognized in carefully controlled trials because they are infrequent or late occurring. They can provide us with insights about rare patient types or symptom presentations that no one center or clinic sees often enough to learn much about. Registries can help us learn from each other, and take quality improvement steps to adopt best practices and remedy poor performance. They can help us identify factors that drive up healthcare costs without adding commensurate health benefits. t is for all these reasons that registries have been proliferating and growing in recent years across the entire spectrum of medicine.[23,24]

A registry on CU specifically would address many of the important gaps in our current knowledge about CU. Its baseline data could provide important information about the triggers, comorbidities, and history of CU, as well as its burden to the patients. Follow-up data could provide important information about the course of the disease, real-world response rates to various treatments actually used in practice, and predictive factors about which patients respond to which treatments. A registry could also provide valuable information – so far almost non-existent in the published literature – about the real-world healthcare utilization of CU patients. We believe the cost of care for CU patients has largely been underestimated and overlooked by government agencies and other healthcare policy makers. Greater awareness of the burden of CU to the healthcare system should lead to greater support for improving treatment and research to reduce that burden. Further information about the need for a CU registry has been published previously.[25]

Although patient registries are rapidly expanding in the medical world,[23,24] including for dermatology and allergology,[26,27] their use on CU has been sparse until now. A recent paper reported on all 12185 CU patients in the Danish National Patient Registry seen from 1994 to 2015 at all 5 specialized dermatology clinics there, and compared them 1:10 to demographically matched non-CU controls from the general population.[28] Compared to controls, CU patients had higher odds ratios (ORs) for a baseline diagnosis of mastocytosis (OR 171.0), anaphylaxis (OR 7.6), allergic rhinitis (OR 5.4), vitiligo (OR 5.4), atopic dermatitis (4.7), and lupus erythematosus (OR 4.7), among others. Although this very large study

provided useful information, it was based on a general patient registry in Denmark. So it may not be generalizable to other regions of the world, and it seems unlikely that more publications about CU will be generated from it.

A multinational Latin American CU registry (N=300) recently reported that 60% of patients had moderate to unbearable pruritus, and 40% had moderate to unbearable CU-related anxiety, both according to the Chronic Urticaria Quality of Life Questionnaire (CU-Q_2oL).[29] Disappointingly, they also reported that 71% of patients did not achieve sufficient control with antihistamines.[29] Although the Latin American CU registry has provided important information, it was available only in Latin American countries, retrospectively collected data on patients only at one timepoint per patient, excluded patients with CIndU only, and is not yet much larger than most studies in the literature.[25,29] The Latin American registry is still active, and we strongly encourage everyone in the region to participate in it, because registries need to reach large sample sizes or completely enroll all patients from the participating centers to fulfill their purposes.

CURE is well positioned to build on the important contributions of these previous registry publications. CURE was founded precisely to provide rigorous scientific data about the symptom patterns, comorbidities, trigger and risk factors, treatments used, responses to treatment, and healthcare utilization of the full spectrum of CU patients seen in real clinical settings around the world. We plan to publish initial statistics this year about the baseline medical characteristics of the patients enrolled, especially the symptom patterns and risk factors. In subsequent years, we will analyze the treatment responses and costs to the healthcare system. Deeper analyses of some of the rarer subtypes of CU may also be performed in the future. Publications from CURE will lead to improvements in the treatment of CU patients by providing greater scientific insight into the many real-world factors involved.

Methods

Ethics

This research initiative was initially approved in 2014 by the Ethics Committee of the Charité University Hospital of Berlin Germany (reference number EA1/146/14), and all other contributing sites are required to obtain ethics approval from their own ethics committees prior to joining the registry. A patient's data may be entered into the registry only if he or she has provided written informed consent to participate in the registry. If a patient later withdraws that

consent, no further data for that patient is entered into the registry, and if requested by the patient, all of his or her prior data are deleted from the registry. If the patient is not of legal age, then written informed consent must be obtained instead from his or her parent or legal guardian. Neither participation in the registry nor refusal to participate in the registry alters the treatment of any patient; the registry is a purely observational approach to research. No personally identifying information of any patient is entered into the registry; each physician receives a participant identification number (ID#) for each patient, and the link between those ID#s and patient names is known only to that physician and his or her staff. The patients do not receive any honoraria or other payments for participation in the registry, and participation in the registry has no relationship to billing of the healthcare system or insurance companies.

Funding

So far, CURE has received financial support from the Urticaria Network e.V. (a German non-profit organization existing to promote research of urticaria), the European Academy of Dermatology and Venereology (proposal number 2014-013), and Novartis. These sponsors have not had any involvement in the design or implementation of CURE. CURE is open to further support from any source, and may be modified by sponsors to collect additional types of data to meet new research, regulatory, or healthcare policy needs. Indeed, as explained below, CURE is eager to partner with more sponsors at this time, in order to continue growing this unique resource. However, the financial sponsors have not had, and will not have, any role or influence on the data analyses or publications of CURE.

Research Design

CURE is a prospective, international, multicenter, observational, voluntary registry of patients with CU. CURE has no target date or sample size for closure; it is intended to continue indefinitely. Physician-reported and/or patient-reported data can be collected using paper forms supplied by CURE or through the physician's usual routine ways of collecting clinical information into his or her usual medical record-keeping system. Either way, the data can then be entered later into CURE electronically by the medical team via the internet, as described in more detail below. Data collection is intended to take place at the patient's initial baseline visit and then to be updated about every six months on an ongoing basis.

Patient Population

CURE aims to collect data on all CU patients. Implicitly there is some unavoidable selection of patients: a) data entry is performed by the medical staff of participating physicians, so the patient must be seeing a physician who has chosen to participate, obtained ethics approval, and signed our collaboration agreement (as described below); b) the physician must diagnose the patient as having CU; c) patients (or their legal guardian) must provide written informed consent to participate in the registry (as explained above); and d) the staff of the treating physician must actually enter the patient's data into the registry (i.e. data entry is voluntary, not mandatory and comprehensive for participating physicians). But otherwise, there are no exclusion or selection criteria (e.g. age, nationality, co-morbidities, type of physician or treatment setting, etc.). The electronic data entry system of CURE is in English. Corresponding baseline and follow-up questionnaires for the physician and patient are currently available in English, German, Chinese, Dutch, and Spanish, if participating physicians wish to use them to facilitate data collection for CURE. Centers who wish to join CURE but treat patients in other languages are encouraged to translate the existing forms into their local language.

Recruitment of Centers

Participation in CURE is open to any physician treating CU patients, regardless of location, medical specialty, or type of practice setting. The only prerequisites to participation are: 1) obtaining approval from the local ethics committee, 2) signing the CURE "Collaboration Agreement" with the UNEV, and 3) appointing a Project Manager who is responsible for performing the documentation and data entry for that site. There is no cost to participate in CURE, nor is there any financial compensation for participation. So far, recruitment of centers to contribute to CURE has taken place mainly through the GA^{2}LEN network of Urticaria Centers of Reference and Excellence (UCARE; including its meetings, quarterly newsletter, and website (www.ga2len-ucare.com)) and by presentations at major conferences of dermatology and allergology, as well as conferences on urticaria. Word-of-mouth and the CURE website (http://www.urticaria-registry.com/) may also have led physicians to join CURE.

Data Collection

CURE provides paper data collection forms (described in more detail below), for both the physician and the patient, for both baseline and follow-up. Participating physicians may freely choose to use these forms or not during the patient consultation. (Electronic data entry

into the CURE registry is then performed later, as described in more detail below.) The timepoint for follow-up data collection is not specified by CURE, but it is hoped that it would take place about every six months.

Questionnaires

All the CURE questionnaires were developed using an expert consensus approach. They rely mainly on basic, ad hoc, multiple choice or short answer questions. They are meant to help the participating centers collect data, but they are not mandatory. Although data on the actual completion time is not available, the questionnaires were designed with the intention that they could be completed in 30 minutes for baseline and 20 minutes for follow-up.

The physician and patient versions of the questionnaires are essentially the same, just worded differently for their respective users. Furthermore, the patient questionnaire starts with several pictures and descriptions of wheals and angioedema, to help ensure that the patient understands which is which. The CURE database only allows entry of one set of answers per patient, regardless of whether the data was collected with the physician questionnaire or the patient questionnaire.

The CURE website (http://www.urticaria-registry.com/for-participants.html) contains copies of all the currently available data collection forms in several languages. The baseline questionnaire has about 60 items that collect data on the patient's demographics, history, symptoms, trigger and risk factors, co-morbidities, past and present therapies, and healthcare utilization. The follow-up questionnaire has about 38 items that collect data about changes of the patient's symptoms, treatments, and healthcare utilization since the last consultation. Both the baseline and follow-up patient questionnaires include the Urticaria Control Test (UCT), a validated questionnaire about the control of urticaria during the past 4 weeks, with 4 questions, each using a 5-point Likert scale.[30,31]

In the data entry system (described below), it is also possible to enter further data for specific diagnostic tests, the familial history of urticaria, the Urticaria Activity Score of 7 days (UAS7),[31-34] the Chronic Urticaria Quality of Life Questionnaire (CU-Q_2oL),[5,31,35] and/or the Dermatology Life Quality Index (DLQI),[36-38] but so far, CURE has not provided the paper questionnaires for these patient-reported outcomes as part of the standard expected data collection, because they are not applicable to all patients and all clinical situations.

Data Entry

So far, all data entry into the registry is performed by the medical staff of the treating physician, via a secure internet webpage, at a timepoint after the actual data collection on paper (as described above). The registry uses secuTrial software (interActive Systems; Berlin, Germany), a secure medical reporting software system that is compliant with the Good Clinical Practice quality standards and with the US Food and Drug Administration's Code of Federal Regulations, Title 21, Part 11. The databases are hosted and administered by the Coordination Center for Clinical Studies of the Charité - Universitätsmedizin Berlin, Germany. Data entry is password protected and uses 128-bit SSL encryption. The secuTrial system has an audit trail system that can be used to track and analyze data entry and any subsequent changes to it. Participating physicians are responsible for retaining all source data.

Data Access

Participating physicians may analyze and publish their own data. To obtain a spreadsheet of their own raw data, the physician submits a "Request for Analysis" to the UNEV, 3 months in advance of the date the data is needed. Participating physicians do retain the right to independently analyze, present, and publish their own data without the approval of the CURE International Steering Committee (ISC), on the condition that they acknowledge the CURE project's role in the research design, data collection, and project management. Specific statistical analyses of the entire CURE database may also be proposed by any physician who has contributed a minimum number of baseline datasets to CURE (currently 30). But these publications are then managed by the CURE ISC, with the proposing physician as a co-author.

International Steering Committee

Decisions about the overall collection, analysis, and publication of data from CURE are made by the CURE ISC. Since CURE is intended to be a worldwide registry, the ISC is structured to avoid more than one member per country. ISC members must declare all potential conflicts of interest. Membership on the ISC is for a renewable period of two years. The ISC members do not receive any payments for their service on the ISC. Physicians contributing to CURE may apply to join the ISC; a two-thirds majority vote of the current ISC is required to add a new member to the ISC. The CURE website (http://www.urticaria-registry.com/) provides the names and contact information of the ISC and the "ISC Charter" document that describes their roles and responsibilities, as well as the rules that guide the publication process for research from CURE.

Limitations

CURE has all the usual limitations of observational research in general and registries in particular. Furthermore, CURE has some of its own specific limitations that should be kept in mind. First, most of the participating physicians have comparatively high specialization for urticaria. So the patients entered are probably more severe and intractable on average than urticaria patients seen in other settings, such as general practice, pediatrics, or pharmacies. The results from CURE may not be applicable to milder forms of urticaria seen in primary care or community settings. Second, the participating physicians are under no obligation to consecutively register all their urticaria patients, and in fact most of them do not. So there is probably unintended selection bias of which patients are registered. Because CURE has this unavoidable but unspecified selection bias, CURE cannot be used to provide definitive epidemiological results on the prevalence or rates of anything in the urticaria population. Third, although CURE is a worldwide registry, a substantial portion of the patients entered so far are from just a few geographically neighboring countries, as described in more detail below. So the results will probably not always be generalizable to patients in other regions of the world. We will be making efforts to recruit more physicians from regions of the world that are currently underrepresented in CURE. Fourth, the data entry into the registry takes place separately from and after the original data collection, and we have not yet audited the accuracy and completeness of the data entry. It is possible that errors are being made in the data entry process or available data is not actually being entered. Time and funding permitting, we intend to perform such data audits in the near future. Fifth, collecting and entering follow-up data is not compulsory, and we have not yet assessed how often follow-up data actually becomes available in CURE. It is entirely possible that the rate of collection and entry of follow-up data is not yet sufficient to be able to analyze and report patient outcomes or other longitudinal results. We intended to assess that later this year.

Upcoming Developments

We are currently testing an electronic patient-reported data capture system. This system would solve many of the limitations mentioned above. It would virtually eliminate all data entry errors, by making data collection and data entry a single identical process performed by the patient. This electronic patient-entered data collection system will also substantially reduce the work burden of the participating centers, and therefore will hopefully also greatly reduce the patient selection bias, which arises because physicians' staff do not have sufficient time to

enter the data for all urticaria patients seen. For the same reason, it would probably ensure follow-up data is collected from every patient who has baseline data in the registry and comes for a follow-up visit.

Further Information

The CURE website (http://www.urticaria-registry.com/) provides a variety of further information, including a "Project Plan" document from July 2016, which contains further information about CURE's aims, design, patient population, ethics, administrative matters, and other such related information.

Initial Implementation

CURE is not just another patient registry – it is a landmark achievement of the global urticaria medical community that has come together over the past couple of decades. In the 20th century, urticaria was (and often still is) a neglected and disliked disease, with a high prevalence and burden in the population[11] but very few specialists dedicated to urticaria and not much interest from governments, the media, or the general public. The field was fragmented among various medical specialties that rarely communicated with each other, including dermatology, immunology, allergology, internal medicine, and pediatrics, with many patients also using emergency room services or consulting general practitioners, psychotherapists, pharmacists, school nurses, and alternative healers. Urticaria research was (and still is) underfunded,[39] and companies had relatively little interest in developing new treatments. It was crucial for the urticaria community to join efforts, and CURE is one landmark demonstration of how well that worldwide collaboration has succeeded this century.

This global networking and collaboration started 20 years ago with the international "Urticaria 2000" conference and its consensus report,[40] which became the prototype for subsequent guidelines. At the time, the field was very much characterized by different "schools" ("urticaria is food intolerance" versus "urticaria is an allergy" versus "urticaria is due to infection" versus "urticaria is an autoimmune disease", and so on), and these schools did not really interact with each other. Since the first version of the guideline,[32] it has been updated three times,[1,34,41,42] with the fourth update currently in process. PURIST, the first international prospective study to characterize the underlying causes of CSU,[43] was a second big step in bringing the urticaria community together. The third big step was the founding and

implementation of the UCARE network,[44] which now has more than 100 UCAREs around the globe and is currently in the process of preparing its first official full publications. Meanwhile, all this collaboration has also led to a substantial increase of efforts from the pharmaceutical industry to develop new and better treatments for CU. CURE has been developed over the past several years, with ethics approval in 2014 and the first patient entered in December 2015. The database has grown steadily over the years (**figure 1**). Its maturation now as a registry with sufficient data to start publishing major papers is the fourth big step in uniting urticaria specialists around the world to our common goal of reducing the burden of CU on our patients. So far, 39 centers around the world have joined CURE and 35 entered baseline data on a total of 2946 patients, as of 26 February 2020 (**table 1**).

The CURE ISC has already planned several forthcoming papers from the data that has already been collected. Currently, we intend that the next publication will be an analysis of the baseline data for patients with CSU only versus patients with CIndU only versus patients with both CSU and CIndU. After that, the next paper will be a comparison of CSU patients with wheals only vs. CSU patients with wheals and angioedema vs. CSU patients with angioedema only. These two papers will help to better define the differences among CU patients, so treatment approaches can be better customized. Participating physicians may also initiate further papers using the data from their own patients, as explained above.

Conclusions

The CURE project is a major research undertaking that has the potential to dramatically improve our knowledge of CU and our patients' medical outcomes. We are eager to have more physicians from around the world join CURE and to provide data on their patients to help improve the lives of urticaria patients. More information about joining and supporting CURE can be found on the website (http://www.urticaria-registry.com/).

Registries are very cost-effective forms of research for the volume and value of their output, but nonetheless they do require substantial financial support.[23,24,26] The CURE registry will lead to major improvements in patient health by providing: 1) better scientific knowledge about this puzzling disease and therefore better treatment, 2) a basis for quality improvement measures in real-world practice, 3) monitoring of potential rare and long-term safety issues, 4) insights into the healthcare costs of CU, and 5) a basis for improved healthcare policy on CU.

Now more than ever, research funding is urgently needed to keep this unique worldwide urticaria project moving forward.

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Figure Legends:

Figure 1. Total number of patients enrolled in CURE over time.

Table legends:

Table 1A. Distribution of enrolled patients, according to the 7 geo-epidemiological super-regions of the Global Burden of Disease study.[45]

Table 1B. Country-level distribution of the enrolled patients (n=1399) from the High Income super-region of table 1A. The percent column is based on the total CURE enrollment (N=2946).

Table 1C. Country-level distribution of the enrolled patients (n=1001) from the Central European, Eastern European, and Central Asian super-region of table 1A. The percent column is based on the total CURE enrollment (N=2946).

Table 1A. Distribution of enrolled patients, according to the 7 geo-epidemiological super-regions of the Global Burden of Disease study.[45]

GBD Super-Region	**n**	**%**
High Income	1399	47
Central Europe, Eastern Europe, and Central Asia	1001	34
Middle East and North Africa	230	8
Southeast Asia, East Asia, and Oceania	136	5
Latin America and Caribbean	89	3
Sub-Saharan Africa	56	2
South Asia	35	1

Table 1B. Country-level distribution of the enrolled patients (n=1399) from the High Income super-region of table 1A. The percent column is based on the total CURE enrollment (N=2946).

Country	**n**	**%**
Germany	616	21
Spain	271	9
France	226	8
Japan	98	3
Argentina	81	3
Netherlands	47	2
Italy	42	1
Portugal	18	1

Table 1C. Country-level distribution of the enrolled patients (n=1001) from the Central European, Eastern European, and Central Asian super-region of table 1A. The percent column is based on the total CURE enrollment (N=2946).

Country	**n**	**%**
Russia	461	16
Poland	378	13
Slovenia	157	5
other Central European	5	0