Evidence Generation of Digital Health Applications in Germany – An Overview of the Status Quo

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Kim-Sarah Krinke[1], Janina Röhrkaste[1], Sebastian Braun[1]
[1]Xcenda GmbH, Hannover, Germany

BACKGROUND

- While in Germany progress in digitization was lacking for many years, in December 2019 the Act to Improve Healthcare Provision through Digitalization and Innovation (Digital Healthcare Act, DVG) came into force and paved the way for the implementation of several digital solutions in the German Statutory Health Insurance (SHI). Amongst others, it enabled digital health applications (DiGA) to be prescribed by doctors or psychotherapists and to be reimbursed by the SHI.[1]
- DiGA are CE-marked smartphone apps or browser-based web applications that can be used to improve the recognition, monitoring, or treatment of a wide range of illnesses, injuries, or disabilities.[2]
- To be reimbursed, DiGA are required to pass an assessment of the Federal Institute for Drugs and Medical Devices (BfArM). A successful assessment leads to a listing in a directory of reimbursable DiGA[3], enabling healthcare providers to prescribe the DiGA and therefore making it easily accessible and free of charge for millions of individuals covered by the SHI system.
- During the assessment procedure, the BfArM determines whether a DiGA fulfills all requirements regarding necessary product qualities (e.g., data protection specifications, safety, and functionality) as well as whether the DiGA use results in a positive healthcare effect.[2]
- Positive healthcare effects can either be a medical benefit (e.g., an improved health status or a shorter disease duration) or a patient-relevant improvement of healthcare structures and processes (e.g., facilitated access to care, improved patient autonomy, or disease coping strategies).[2]
- To prove a DiGA's positive healthcare effect, manufacturers must provide quantitative results of a comparative study conducted in Germany. This study needs to demonstrate the superiority of using the DiGA over not using it in terms of at least one claimed positive healthcare effect.[2]
- If the DiGA manufacturer can present such a study, an application for a final listing in the DiGA directory is suggested. In case of a positive assessment decision by the BfArM, the DiGA will become accessible in the directory no later than three months after application.[2]
- If the manufacturer is not yet able to present a study sufficient to prove a positive healthcare effect, the DVG enables an application for a provisional listing in the DiGA directory. Nevertheless, it needs to show the DiGA's product quality as well as include systematically evaluated data generated within a pilot study using the DiGA and demonstrating a likely positive healthcare effect.[2]
- The DiGA will become accessible in the directory as soon as the BfArM approves the provisional listing, marking the beginning of a one-year test phase during which the study results for final listing can be submitted. In case of missing study results or a negative decision by the BfArM at the end of the test phase, the DiGA will be deleted from the directory.[2]

OBJECTIVE

- This research aimed at aggregating evidence provided by the manufacturers of a DiGA for the provisional or final listing in the DiGA directory.

METHODS

- All DiGA in the directory accessible until September 30th, 2022 were screened by two independent researchers.
- DiGA were analyzed regarding their timepoint and type of listing (provisional vs. final vs. deleted), therapeutic area and claimed positive healthcare effects.
- Special attention was given to the evidence that was generated in submitted studies, including the study type, study population size, and study period.

RESULTS

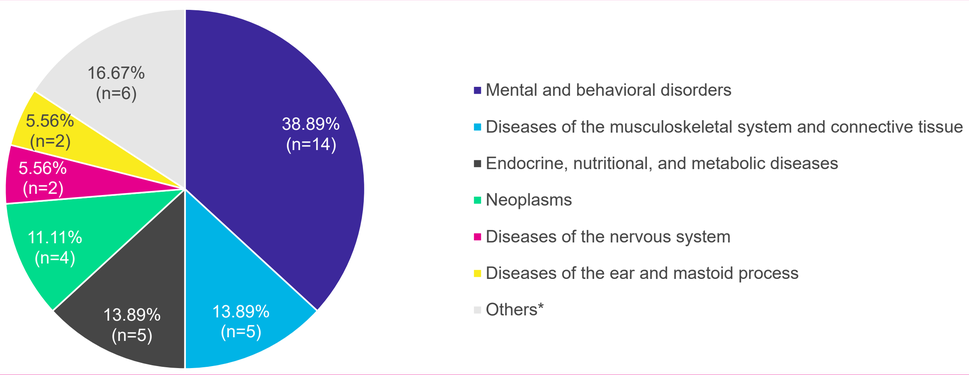
- As of September 30th, 2022, N=36 DiGA were publicly available in the directory. Thereof, n=12 (33.33%) DiGA were listed finally, and n=21 (58.33%) provisionally. Another n=3 (8.33%) DiGA were deleted from the directory and are thus no longer reimbursable. While only one of these three DiGA was deleted after a negative assessment decision by the BfArM following the one-year test phase, two DiGA were deleted at the request of the respective manufacturers.
- With the launch of the directory in September 2020, the highest number of DiGA (n=9) was listed in the fourth quarter 2020 (see Figure 1). Subsequently, the number of DiGA included in the directory varied over time with n=2 to n=7 DiGA per quarter being listed.

Figure 1. Final and provisional listings in the DiGA directory over the course of time

Please note, DiGA that were deleted following provisional listing in the directory are included in the figure.

- The by far largest proportion (n=14, 38.89%) of all listed DiGA targeted mental and behavioral disorders such as depression, anxiety, tobacco addiction, or alcohol dependency (see Figure 2). The second most common therapeutic areas were diseases of the musculoskeletal system and connective tissue (e.g., gonarthrosis or arthrosis of the spine) as well as endocrine, nutritional, and metabolic diseases (e.g., diabetes or obesity). Other DiGA were designed to help patients coping with neoplasms (e.g., breast cancer), diseases of the nervous system (e.g., multiple sclerosis or migraine) or diseases of the ear and mastoid process (e.g., tinnitus), for example.

Figure 2. Targeted therapeutic areas of all listed DiGA in the directory (N=36)

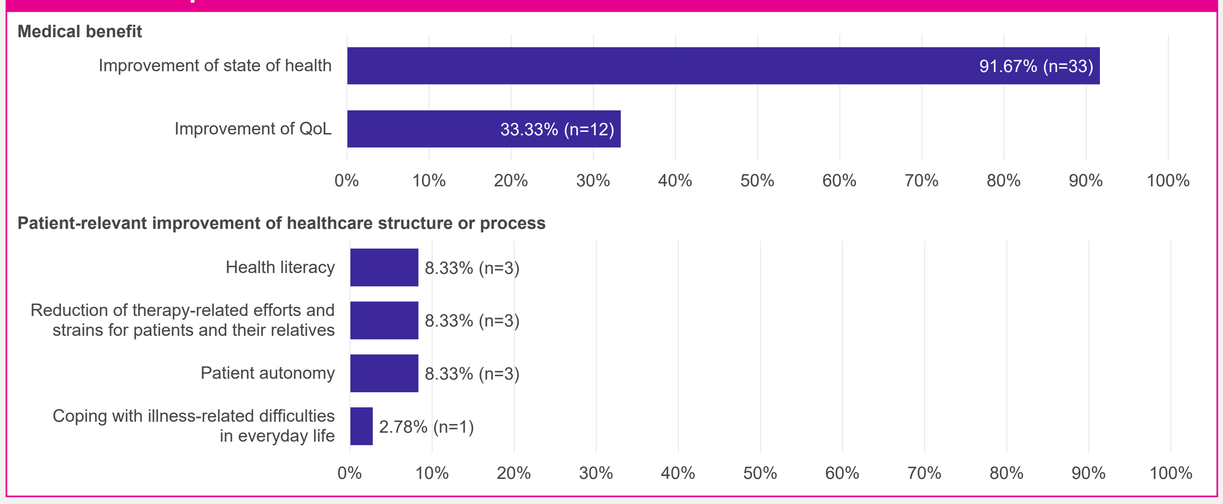


*Therapeutic areas that were targeted by n=1 DiGA each, were summarized as "others". This category includes diseases of the digestive system, nervous and circulatory system, and genitourinary system, symptoms affecting speech and voice, symptoms and abnormal clinical and laboratory findings not classified elsewhere as well as factors influencing health status and leading to health care utilization.

RESULTS (CONTINUED)

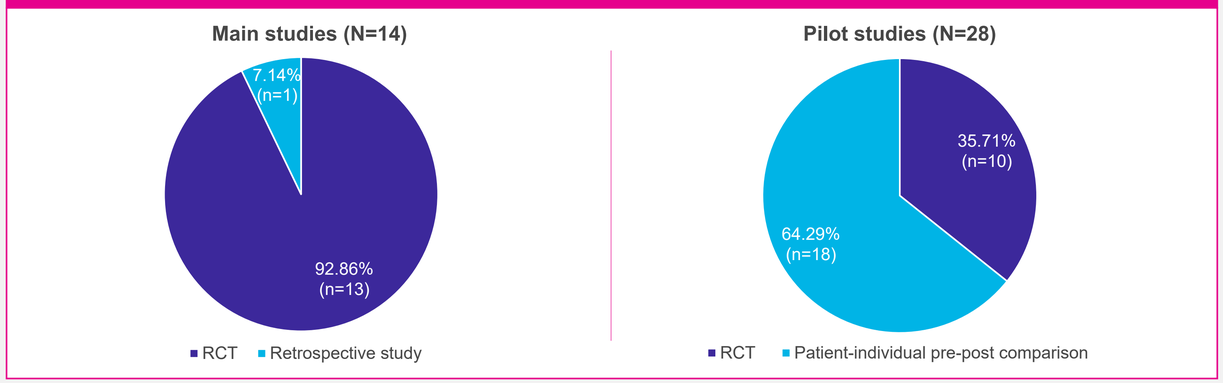
- Nearly all (n=35, 97.22%) DiGA claimed at least one medical benefit. In particular, n=33 (91.67%) DiGA claimed to improve the state of health and n=12 (33.33%) DiGA claimed to improve the quality of life (QoL) of patients in their target population. To date, none of the DiGA listed in the directory aimed at the prolongation of survival or the reduction of the duration of a disease, which were suggested as potential positive healthcare effects by the BfArM (see Figure 3).
- Only one DiGA did not claim any medical benefit, but only a patient-relevant improvement of healthcare structures and processes. Another six (16.67%) DiGA also claimed patient-relevant improvement of healthcare structures and processes beyond a medical benefit. Specifically, health literacy, patient autonomy, and/or the reduction of therapy-related efforts and strains for patients and their relatives were each targeted of n=3 (8.33%) DiGA. Furthermore, n=1 (2.78%) DiGA aimed to improve coping with disease-related difficulties in everyday life (see Figure 3).

Figure 3. Claimed medical benefits and patient-relevant improvements of healthcare structure or process



- Overall, N=14 comparative studies submitted for final listing were reviewed, as two manufacturers each provided two comparative studies for their DiGA. Thereof, almost all studies (n=13) were designed as randomized controlled trial (RCT), while n=1 retrospective data analysis was conducted. However, the retrospective data analysis was provided along with an RCT.
- In total, N=28 pilot studies were examined since some manufacturers conducted more than one study to demonstrate a likely positive healthcare effect. More specifically, two pilot studies each were provided for n=2 DiGA and three pilot studies were submitted for n=1 DiGA. The majority of pilot studies was considered patient-individual pre-post comparisons (n=18). Still, n=10 RCTs were conducted to achieve a provisional listing in the DiGA directory (see Figure 4).

Figure 4. Study types for evidence generation in main and pilot studies



- Population sizes varied between 20 and 797 participants in the pilot studies and between 56 and 1,013 patients in the main studies (see Table 1).

Table 1. Population size in main and pilot studies

	Main studies (N=14)		Pilot studies (N=28)	
	summary statistics, n	%	summary statistics, n	%
Sum	4,065		4,354	
Mean	290.36		155.50	
Min	56		20	
Q1	169		50	
Median	207		75	
Q3	272		205	
Max	1,013		797	
0-29 participants	0	0.00	1	3.70
30-99 participants	2	14.29	15	55.56
100-199 participants	3	21.43	4	14.81
200-299 participants	6	42.86	4	14.81
300-399 participants	0	0.00	1	3.70
400-499 participants	1	7.14	2	7.41
≥500 participants	2	14.29	1	3.70

Max: Maximum; Min: Minimum; Q1: First quartile; Q3: Third quartile.

- The follow-up period of the main studies spanned between three and twelve months with most studies having a follow-up of six months (n=9). The follow-up period of the pilot studies varied between four weeks and two years. However, almost 40% of the pilot studies (n=11) assessed outcomes after a follow-up period of twelve weeks.

CONCLUSIONS

- Studies to demonstrate positive healthcare effects and thus final listing in the DiGA directory are usually designed as prospective studies with a trend to RCTs, especially for studies that are submitted for final listing. However, the specific study design and evaluation methods strongly depend on the type of DiGA and the intended positive healthcare effect.
- Even though it is no mandatory requirement for final listing in the DiGA directory, most of the manufacturers provide evidence generated in RCTs to demonstrate positive healthcare effects. The successful completion of these studies is fundamental for a final listing in the directory and, accordingly, reimbursement by the SHI.

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