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Patient Listening on Social Media for Patient-Focused Drug Development: a synthesis of considerations from patients, industry and regulators

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Abstract

Patients, life science industry and regulatory authorities are united in their goal to reduce the disease burden of patients in order to close remaining unmet needs. Patients have however not always been systematically and consistently involved in the drug development process. Recognizing this gap, regulatory bodies worldwide have launched patient-focused drug development initiatives to foster a more systematic involvement of patients in the drug development process and to ensure that outcomes measured in clinical trials are truly relevant to patients and represent significant improvements to their quality of life. Social media has been consistently shown to capture the first hand, spontaneous and unfiltered disease and treatment experience of patients and is acknowledged as a legitimate method for generating patient experience data by the FDA. While Social Media Listening methods are increasingly applied to many diseases and use cases, a significant piece of uncertainty remains on how evidence derived from social media can be used in the drug development process and how it can impact regulatory decision making. In this policy paper we review the perspectives of three key stakeholder groups on the role of social media listening in drug development. We carry out a systematic review of current best practices and use cases for SML and in particular highlight benefits and drawbacks for the use of SML as a way to identify unmet needs of patients. We analyze the perspectives of patients, life science companies and regulatory authorities on the basis of publicly available information. While we find that the stakeholders are strongly aligned regarding the potential of social media for PFDD, we highlight six key areas in which regulatory

guidance is needed to reduce uncertainty regarding the impact of social media analysis as a source of patient experience data that has impact on regulatory decision making.

1 Introduction

Patients have direct and first-hand experience and knowledge of which symptoms are most burdensome and how the condition affects their daily living, which makes them experts on many aspects of their condition (ICH 2021). Moreover, they are able to judge their level of unmet need, that is the gap between the concerns and problems that are addressed by existing treatments and those that remain unsolved. An important goal for drug development is to narrow down this gap and continuously increase the quality of life of the patients. Thus, it has been noted that there is a significant need for more involvement of patients in drug development, in particular in activities related to research prioritization, target product profile development, trial design, regulatory approval, access to medicines, reimbursement, and treatment decisions, which all profit from alignment with the needs of patients (Lowe et al. 2016; Haerry et al. 2018). For instance, an important measure to make drug development more patient-centric is to ensure that trial outcomes are relevant, appropriate and of importance to patients in real-world settings (Anderson and McCleary, 2015, Bartlett et al. 2014, Boutin et al. 2017, Lowe et al. 2016, Morel and Cano 2017). It has been emphasized that this involvement needs to be from early on, ideally already in research prioritization as well as when developing a product strategy, in order to unfold maximal impact (Lowe et al. 2016; Haerry et al. 2018).

Regrettably, patients have not always been systematically, consistently, and continuously involved in the drug development process (Carson 2022). Indeed, many trials fail to translate into benefits for patients (Heneghan et al. 2017). In a review of 57 dementia drug trials, Molnar et al. (2009) found that less than half (46%) of the trials discussed the clinical significance of their results. In many cases, outcomes that are accepted by regulators (e.g. the 6 minute walking test) do not correspond to any real improvement to the patient. A systematic review regarding the inclusion of patient-reported outcomes in cardiovascular trials showed that only 23% out of 413 analyzed trials indeed included outcomes of importance to patients. In 40% of these cases, included PROs were judged to be of little value (Rahimi et al. 2010). 70% of trials were missing data relevant to judge the clinical meaningfulness of results. The lack of systematic inclusion of patient voices in drug development is a missed opportunity with respect to the goal of developing treatments that truly improve patients' lives, based on a systematic understanding of what challenges they face in their daily lives and the tradeoffs they are willing to accept. It is thus an important goal to ensure that trials are designed and conducted in such a way that they maximize treatment benefit for patients and address existing unmet needs.

In recognition of this situation, there is consensus among regulators worldwide that a more systematic approach to patient involvement in drug development is needed in order to maximize treatment benefit and facilitate treatment uptake by patients. The Food and Drug Administration (FDA) for instance, has established the Patient-focused drug development (PFDD) initiative (Mullin 2013). With a series of 4 guidance documents, the FDA is seeking to provide clarification on how *patient experience data* can be collected and analyzed to ensure that outcomes of clinical trials are indeed relevant and meaningful from the patient perspective. These guidelines include recommendations on methods for data collection (Guidance 1), and methods for determining what is important to patients (Guidance 2). Guideline 3 on how to select, develop or modify fit-for-purpose clinical outcomes assessments is available as a draft since June 2022. Guideline 4 on incorporating clinical outcome assessments into endpoints for regulatory decision-making is available as a draft

since April 2023. Other agencies have followed with similar initiatives. The EMA has stressed the importance of patient involvement in drug development as part of its 2025 strategy (EMA 2020). The MHRA has also published a corresponding strategy for increasing patient involvement in drug development (MHRA 2021) and started a pilot requesting sponsors to submit patient experience data as part of their applications.

The FDA has explicitly mentioned some aspects of patient experience data that are relevant for PFDD:

- Impact of the disease and its treatment on the patient (symptoms, chief complaints, burden of living with the disease/condition)
- Patients' perspectives about potential and current treatments (expectation of benefits, tolerance of risks, acceptable tradeoffs)
- Views on unmet medical needs and available treatment options
- Enhanced understanding of the natural history of the disease or condition

Social media has been shown to capture and provide patient insights of relevance to all the dimensions mentioned above (Schmidt et al. 2022). Thus, social media has been specifically mentioned in the guidelines of the FDA as an important source to passively collect patient experience data and to incorporate the voice of patients in drug development by analyzing the experiences they share in social media sites both qualitatively and quantitatively. Yet, there remain significant gaps and uncertainties in the understanding of how social media data can be systematically incorporated into drug development and, most importantly, which role it can play in approval processes.

The goal of this paper is to contribute to understanding the role that social media listening can play in order to leverage patient experience data collected from social media for patient-focused drug development. The paper reviews the current considerations of key stakeholders: patients, industry and regulators. Based on an analysis of these perspectives, it attempts to provide a synthesis of these, and defines key questions that need to be addressed in future work towards establishing social media listening as a sound and robust source of patient experience data that impacts regulatory decision making.

2 Social Media Listening

Social Media Listening (SML) refers to a set of observational methods comprising the passive identification, collection and analysis of patient experience data from online data sources, social media in particular. In contrast to other more established methods such as HRQoL surveys, 1-on-1 interviews, focus groups etc. these methods are passive in the sense that they neither require nor allow for a direct interaction with patients, who can remain fully anonymous.

SML is an active area of research with many mature methodologies having been developed to date. In order to summarize the current work and focus in SML as part of this article, a literature review has been conducted by querying PubMed and Embase for articles mentioning the keywords "social media" and "patient", plus one of the keywords "listening" or "monitoring" in the title or abstract, while excluding either of "survey", "engage", "recruit", "recruitment" or "use". These keywords were selected to ensure that the investigated articles focus on patient listening studies from social media sources, rather than using social media as recruitment, engagement or dissemination channels

for studies following different methodological settings. Likewise, studies focusing on different behaviors in social media use were excluded as well. The publication date was set to an interval ranging from 2015 to February 2023. Applying this search strategy, 177 publication records were identified and investigated following the PRISMA approach (Page et al. 2020) as shown by the flow diagram in Figure 1. As an outcome of the screening procedure, a selection comprising 63 relevant articles was included for in-depth review, the main findings of which are summarized in Figure 1 below.

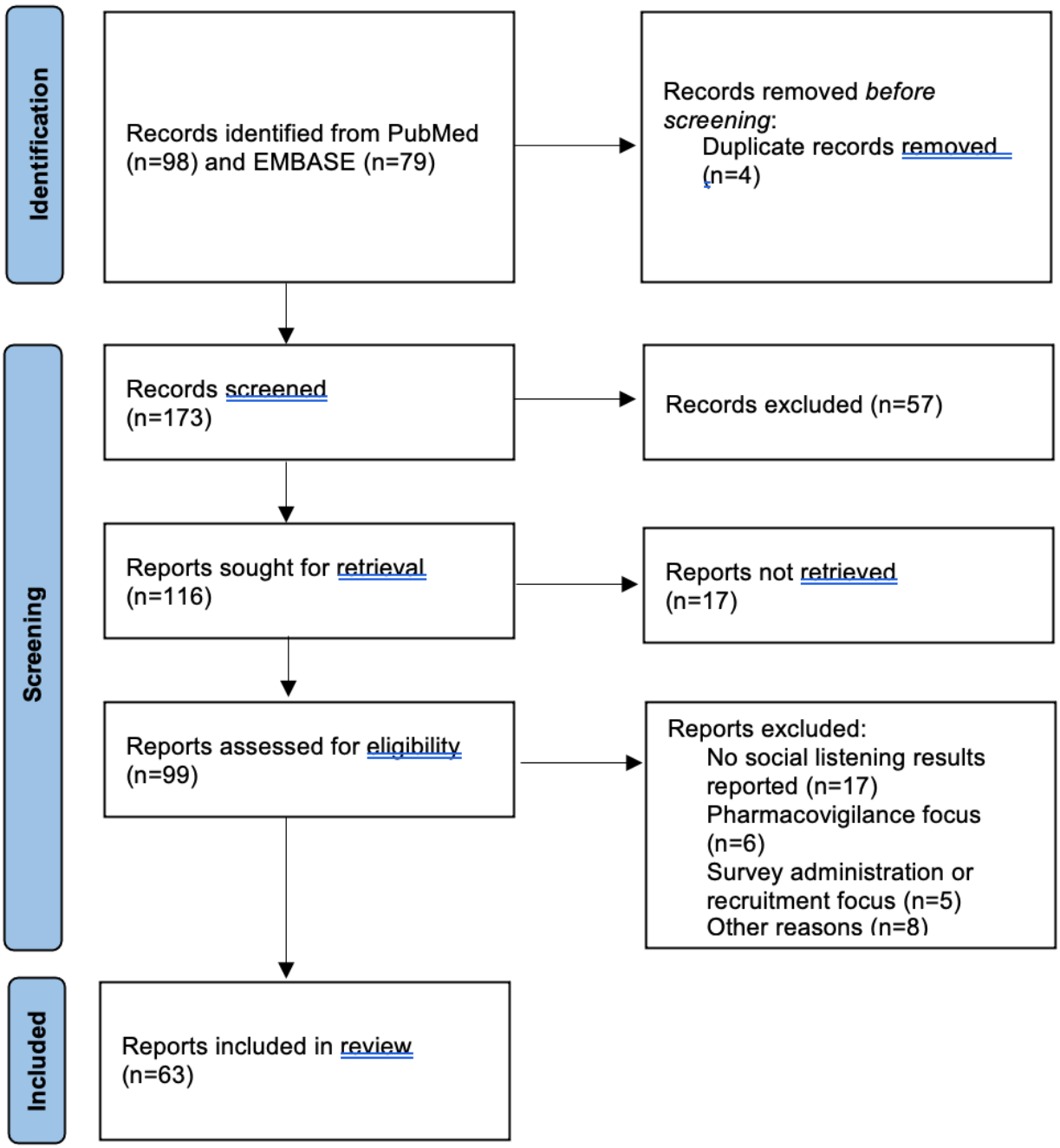

Figure 1: Overview of screening procedure followed in conducting the literature review (based on PRISMA approach; cf. Page et al. 2020)

Social media listening has been applied to a variety of indications including but not limited to *Chronic Kidney Disease* (James et al. 2020), *Schizophrenia* (Hswen et al. 2018), *Multiple Sclerosis* (Donkers et al. 2020), *Melanoma* (McDonald et al. 2019a, Tadmouri et al. 2022), *Metastatic Breast Cancer* (Shimkhada et al. 2021), *Psoriasis* (Reuter and Lee 2021), *COPD* (Cook et al 2018., Patalano et al. 2020), *Multiple Myeloma* (Gries and Fastenau 2020), *Dry Eye Disease* (Cook et al. 2019b), *Tardive Dyskinesia*, (Farrar et al. 2021), *Acute Myeloid Leukemia* (Booth et al. 2019), *Crohn's* (Bichteler et al. 2019), *Obesity* (Hartung et al. 2021), and *Bronchiectasis* (Delestre-Levai et al. 2021).

In terms of social media sources, the most widely used are Twitter (Adobes-Martin et al. 2021, Cook et al. 2019a, Delestre-Levai 2021, i.a.), online forums (Delestre-Levai et al. 2021, Dobson et al. 2022, Rodrigues et al. 2022, i.a.), Facebook or closed networks (Cotte et al. 2020, Delestre-Levai et al. 2021, Emmott et al. 2021, i.a.) and patient communities (Crawford et al. 2020, Dave et al. 2019, Faust et al. 2022). More recently, studies have also started to use Reddit as a data source (Dobson et al. 2022, Flurie et al. 2022, Perella et al. 2023, i.a.). Youtube and Instagram have also been used in the last 2-3 years (Cotte et al. 2020, Crawford et al. 2020, Dobson et al. 2022, He et al. 2021, Silverberg et al. 2022, i.a.).

Social media patient listening has been used by a number of drug sponsors including AstraZeneca, Boehringer Ingelheim, BMS, Chiesi, GSK, Horizon Therapeutics, Johnson & Johnson, Merck, Neurocrine Biosciences, Novartis, Novo Nordisk, Pfizer, Pierre Fabre, Roche, Sanofi, UCB.

Indications	**Goals/Objectives**	**Sources**	**Sponsors**
Acute Myeloid Leukemia (Booth et al. 2019) **Amblyopia** (Syntosi et al. 2022) **Ankylosing spondylitis** (Minhas et al. 2017) **Atopic dermatitis** (Silverberg et al. 2022, Voillot et al. 2022) **Bronchiectasis** (Delestre-Levai et al. 2021) **Cancer** (Cotte et al. 2020) **Chronic Kidney Disease** (James et al. 2020) **Chronic ocular pain** (Goel et al. 2022)	**Analyze online communication behavior and influence of key opinion leaders** (Lynn et al. 2020, Taylor et al. 2018, Wolffsohn et al. 2020) **Barriers to care** (Shimkhada et al. 2021, Miyake & Martin 2021) **Common mental health symptoms** (Hswen et al. 2018, Flurie et al. 2022) **Disease burden, key symptoms** (Patalano et al. 2020, Chauhan et al. 2022, Crawford et al. 2020, Silverberg et al. 2022, Goodspeed et al. 2023, Hasan et al. 2022, Lan et al. 2021, Mazza et	**Consumer reviews** (Silverberg et al. 2022) **Facebook** (Cotte et al. 2020, Delestre-Levai et al. 2021, Emmott et al. 2021, Flurie et al. 2022, Goel et al. 2022, Goodspeed et al. 2023, Keller et al. 2018, Lognos et al. 2019, Miyake & Martin 2021, Picone et al. 2020, Rodrigues et al. 2022, Strobel et al. 2022, Tapi Nzali et al., 2017) **Instagram** (Cotte et al. 2020, Silverberg et al. 2022) **News** (Findley et al. 2023, Silverberg et al.	**AstraZeneca** (James et al. 2020) **Boehringer Ingelheim** (Bichteler et al. 2019, Hartung et al. 2021) **BMS** (Cotte et al. 2020, McDonald et al. 2018, McDonald et al. 2019a) **Chiesi** (Delestre-Levai et al. 2021) **GSK** (Merinopoulou et al. 2018,

Complement 3 Glomerulopathy (C3G) (Tyagi et al. 2019a)

COVID-19 / Long COVID (Hasan et al. 2022, He et al. 2021, Miyake & Martin. 2021, Picone et al. 2020)

Crohn's Disease (Bichteler et al. 2019)

Dental medicine (Adobes-Martin et al. 2021, Emmott et al. 2021)

Diseases that require hysterectomy (Dave et al. 2019)

Dry Eye Disease (Cook et al. 2019b)

Eosinophil-Driven Diseases (EGPA & HES) (Strobel et al. 2022)

GI Discomfort (Schäfer et al. 2020)

Gout (Flurie et al. 2022)

Hematologic cancers (Merinopoulou et al. 2018)

Immunoglobulin A nephropathy (IgAN) (Tyagi et al. 2019b)

Inflammatory bowel disease (Keller et al. 2018)

Lung cancer (Rodrigues et al. 2022)

Melanoma (Chauhan et al. 2022, Faust et al. 2022, al. 2022, McDonald et al. 2018, Modica et al. 2017, Perella et al. 2023, Picone et al. 2020, Ping et al. 2016, Qian et al. 2021, Quartey et al. 2018, Rodrigues et al. 2022, Schäfer et al. 2020, Spies et al. 2022, Staunton et al. 2022, Stens et al. 2020, Strobel et al. 2022, Syntosi et al. 2022, Tadmouri et al. 2022)

Emotional impact of disease, diagnosis and treatment (Delestre-Levai 2021, Farrar et al. 2021, Flurie et al. 2022, Goodspeed et al. 2023, He et al. 2021, Voillot et al. 2022, Rezaallah et al. 2019)

HRQoL concepts (Gries and Fastenau 2020, Tapi Nzali et al. 2017, Cotte et al. 2020, Findley et al. 2023, Goel et al. 2022, Perella et al. 2023, Qian et al. 2021, Rodrigues et al. 2022, Spies et al. 2022, Staunton et al. 2022, Syntosi et al. 2022, Tadmouri et al. 2022, Tyagi et al. 2019a, 2019b, Voillot et al. 2022, Wolffsohn et al. 2020)

Identify perceived causes for disease (Goel et al. 2022)

Identify/Predict condition (Ellouze & Hadrich 2022, Hasan et 2022, Syntosi et al. 2022, Tyagi et al. 2019a, 2019b, Wolffsohn et al. 2020)

Online forums, blogs (Cook et al. 2019a, Cook et al. 2019b, Cotte et al. 2020, Delestre-Levai et al. 2021, Dobson et al. 2022, Donkers et al 2020., Findley et al. 2023, Goel et al. 2022, Keller et al. 2018, Lognos et al. 2019, Lundt et al. 2020, Mazza et al. 2022, Miyake & Martin 2021, Perella et al. 2023, Qian et al. 2021, Rezaallah et al. 2019, Rodrigues et al. 2022, Schäfer et al. 2020, Silverberg et al. 2022, Staunton et al. 2022, Strobel et al. 2022, Syntosi et al. 2022, Tyagi et al. 2019b, Tyagi et al. 2019b, Weissenbacher et al. 2021, Wolffsohn et al. 2020)

Patient Communities (Crawford et al. 2020, 2021, Dave et al. 2019, Faust et al. 2022, Frank et al. 2023, Freeman et al. 2021, Gries and Fastenau 2020, Hasan et al. 2022, James et al. 2020, Keller et al. 2018, Mazza et al. 2022, McDonald et al. 2018, McDonald et al. 2019a, Merinopoulou Strobel et al. 2022)

Horizon Therapeutics (Flurie et al. 2022)

Johnson & Johnson (Crawford et al. 2020, Lan et al. 2021)

Merck (Spies et al. 2022)

Neurocrine Biosciences (Farrar et al. 2021, Lundt et al. 2020)

Novartis (Cook et al. 2019a, 2019, Faust et al. 2022, Findley et al. 2023, Frank et al. 2023, Goel et al. 2022, Mazza et al. 2022, Minhas et al. 2017, Modica et al. 2017, Perella et al. 2023, Rezaallah et al. 2019, Rodrigues et al. 2022, Syntosi et al. 2022, Tyagi et al. 2019a, 2019b, Wolffsohn et al. 2020)

McDonald et al. 2019a, Tadmouri et al. 2022)

Metastatic Breast Cancer (Shimkhada et al. 2021, Lognos et al. 2019, Mazza et al. 2022, Ping et al. 2016)

Multiple Myeloma (Crawford et al. 2020, 2021, Gries and Fastenau 2020)

Multiple Sclerosis (Donkers et al. 2020, Dobson et al. 2022, Lan et al. 2021, Rezaallah et al. 2019)

Myelodysplastic syndromes (Frank et al. 2023)

Nutrition (Lynn et al. 2020)

Obesity (Hartung et al. 2021)

Parkinson's disease (Zhang et al. 2021, Qian et al. 2021, Staunton et al. 2022)

Personality disorder (Ellouze & Hadrich 2022)

Presbyopia (Findley et al. 2023, Wolffsohn et al. 2020)

Psoriasis (Reuter & Lee. 2021)

Renal cell carcinoma (McDonald et al. 2018)

al. 2022, Ping et al. 2016, Schäfer et al. 2020)

Impact on caregivers (Farrar et al. 2021, Faust et al. 2022, Frank et al. 2023, Goodspeed et al. 2023, Lundt et al. 2020, Mazza et al. 2022, Modica et al. 2017, Strobel et al. 2022)

Patient-reported experiences, symptoms, outcomes and patient journeys (James et al. 2020, Adobes-Martin et al. 2021, Chauhan et al. 2022, Faust et al. 2022, Findley et al. 2023, Freeman et al. 2021, Goel et al. 2022, Hasan et al. 2022, Mazza et al. 2022, McDonald et al. 2018, Modica et al. 2017, Perella et al. 2023, Picone et al. 2020, Quartey et al. 2018, Rodrigues et al. 2022, Schäfer et al. 2020, Spies et al. 2022, Stens et al. 2020, Strobel et al. 2022, Syntosi et al. 2022, Tadmouri et al. 2022, Tyagi et al. 2019a, 2019b, Crawford et al. 2020, Rezaallah et al. 2019)

Treatment coverage/Treatment experience (Cotte et al. 2020, Dave et al. 2019, Faust et al. 2022, He et al. 2021, McDonald et al. 2018, Merinopoulou et al. 2018, Minhas et al. 2017, Qian et al. 2021,

et al. 2018, Minhas et al. 2017, Ping et al. 2016, Qian et al. 2021, Quartey et al. 2018, Rodrigues et al. 2022, Schäfer et al. 2020, Spies et al. 2022, Strobel et al. 2022, Tadmouri et al. 2022)

Reddit (Dobson et al. 2022, Flurie et al. 2022, Perella et al. 2023, Picone et al. 2020, Silverberg et al. 2022, Strobel et al. 2022)

Tumblr (Dobson et al. 2022, Silverberg et al. 2022, Strobel et al. 2022)

Twitter (Adobes-Martin et al. 2021, Cook et al. 2019a, Cook et al. 2019b, Delestre-Levai 2021, Dobson et al. 2022, Ellouze & Hadrich 2022, Emmott et al. 2021, Farrar et al. 2021, Findley et al. 2023, Goel et al. 2022, Hswen et al. 2018, Karthik et al. 2019, Lundt et al. 2020, Lynn et al. 2020, Mazza et al. 2022, Miyake & Martin 2021, Perella et al. 2023, Quartey et al. 2018, Reuter & Lee 2021, Rodrigues et al. 2022, Shimkhada et al. 2021, Silverberg et al. 2022, Stens et al. 2020, Strobel et al. 2022,

Novo Nordisk (Rodrigues et al. 2022)

Pfizer (Booth et al. 2019, Crawford et al. 2021, Silverberg et al. 2022)

Pierre Fabre (Tadmouri et al. 2022)

Roche (Dobson et al. 2022, Freeman et al. 2021, Quartey et al. 2018, Schmidt et al. 2022, Staunton et al. 2022)

Sanofi (Voillot et al. 2022)

UCB (Zhang et al. 2021)

Sarcoma (Taylor & Pagliari 2018) **Schizophrenia** (Hswen et al. 2018) **SLC6A1 disorder** (Goodspeed et al. 2023) **Sjögren's disease** (Perella et al. 2023) **Systemic juvenile idiopathic arthritis** (Modica et al. 2017) **Systemic Lupus Erythematosus** (Spies et al. 2022, Stens et al. 2020) **Tardive Dyskinesia** (Farrar et al. 2021, Lundt et al. 2020) **Undefined** (Quartey et al. 2018, Weissenbacher et al. 2021)	McDonald et al. 2019a, Rodrigues et al. 2022, Spies et al. 2022, Tadmouri et al. 2022, Voillot et al. 2022, Weissenbacher et al. 2021, Crawford et al. 2020) **Treatment seeking / selection** (Booth et al. 2019, Reuter & Lee 2021, Donkers et al. 2020, Dobson et al. 2022, Frank et al. 2023, Keller et al. 2018, Lognos et al. 2019, Merinopoulou et al. 2018, Minhas et al. 2017, Miyake & Martin 2021, Quartey et al. 2018, Emmott et al. 2021, Rodrigues et al. 2022, Weissenbacher et al. 2021, Rezaallah et al. 2019) **Unmet needs** (Cook et al. 2019a, Zhang et al. 2021, Flurie et al. 2022, Frank et al. 2023, Lundt et al. 2020, Spies et al. 2022, Stens et al. 2020, Tyagi et al. 2019b, 2019b)	Syntosi et al. 2022, Taylor & Pagliari 2018, Tyagi et al. 2019a, 2019b, Weissenbacher et al. 2021, Wolffsohn et al. 2020) **Youtube** (Cotte et al. 2020, Crawford et al. 2020, Dobson et al. 2022, He et al. 2021, Rodrigues et al. 2022, Strobel et al. 2022)	

Table 1: Summary of findings from literature review on published social listening articles since 2015

Most authors have emphasized that SML should not be understood as a substitute for existing research instruments, but as a complement to them (Delestre-Levai 2021, Gries and Fastenau 2020, McDonald et al. 2019a). The main benefit of SML is that it provides access to the first-person, authentic, spontaneous, unbiased and unfiltered perspective of patients, described in their own words (Cook et al. 2019a, Delestere-Levai 2021, James et al. 2020). The fact that we get access to first person author experiences in patients' own words is particularly valuable for PFDD as it facilitates conceptualizing the disease from the patient's perspective by using terms and concepts that reflect their understanding.

It has been shown that SML is often able to reproduce the main symptoms of a disease as identified by more traditional methods, in some cases even identifying symptoms that were not captured in interviews (Humphrey et al. 2017). Going beyond symptoms, SML has the potential to contribute to a more holistic perspective of the disease burden by helping to understand i) the factors that reduce the quality of life of patients (Gries and Fastenau 2020, Tapi Nzali 2017), ii) the social context into which they are embedded as well as iii) their emotional trajectories (Gries and Fastenau 2020, Delestre-Levai 2021). It can provide background to understand treatment seeking and treatment selection behaviour and the main factors involved therein (Booth et al. 2019, Donkers et al. 2020, Reuter et al 2021).

SML allows researchers to track patient perspectives and health trends over time, offering crucial insights into the evolution of diseases and patient experiences (Cook et al. 2019b) and allows to capture evolving insights and trends in real time.

Some authors have emphasized that SML can provide insights about a broader population compared to the more narrow populations considered in clinical trials, as we might be able to capture the perspectives of people that are underrepresented in clinical trials but also the perspectives of family, caregivers etc. in the broader environment of patients. In contrast to many other research methods, SML has the unique advantage of allowing to reach patient populations that traditional healthcare approaches might overlook. For instance, individuals suffering from rare diseases, those who lack access to healthcare due to the absence of a healthcare plan, or patients who have discontinued their treatment for a range of reasons — including dissatisfaction with outcomes, severe side effects, or conditions rendering them incapable of treatment (e.g., psychosis) — can be effectively found via social media. It can help in particular to assess conditions where patient experiences and symptoms may go unreported due to factors such as fear of stigmatization, distrust of healthcare professionals, or personal uncertainty (Webb Hooper et al. 2019). Further, it can help to address diverse and broad populations that might be hard to reach otherwise. Leveraging the expansive reach of social media facilitates the analysis of a diverse and large population sample, hence providing a comprehensive data volume that may be more representative than traditional data collection methods due to the amount of data points and observations related to various aspects of patient's condition.

From a methodological perspective, SML is an observational, non-interventional method that does not rely on a specific set of questions to be asked to patients, in contrast to more traditional instruments (interviews, surveys, focus groups). By avoiding to formulate specific questions beforehand, SML methods avoid problems related to biases that might be created by asking a question in a specific manner (e.g. leading question biases). For this reason, it has been noted that SML is a suitable method to identify what priorities and outcomes are important to patients (James et al. 2020). At the same time, as the method simply observes and analyzes the online behavior of patients, it minimizes the burden and requirements on the patient to contribute their views for PFDD (Cook et al. 2019a). Further, SML represents a very cost-effective and scalable method (Delestre-Levail 2021) that can cover multiple geographies (Cook et al. 2019a).

An inherent limitation of SML is that, in deciding whether to include a patient in a SML study, we rely on the self-disclosed information of patients to decide whether they meet inclusion criteria. The information provided by patients, e.g. on diagnosis, might however be incomplete and inaccurate, leading to uncertainty regarding whether the investigated population really fulfills all inclusion criteria (Delestre-Levai 2021, McDonald et al. 2019a). In particular, demographic information, although in some cases inferable, is not widely and accurately available from social media sources (Hwsen et al. 2018). Methodologically, when using SML, it is thus important to take into account the

fact that there is uncertainty in terms of the extent to which patients fullfill the inclusion criteria. Due to the non-interventional, observational nature of the method, in spite of some comments of patients being unclear or incomplete, there is no possibility for following up or seeking clarification, an inherent limitation of the method (Cook et al. 2019a).

A further important limitation regards the validity of the results obtained with SML and the extent to which they generalize to the target population (Delestre-Levai 2021, McDonald et al. 2019a). In particular, data collection from social media might be affected by several types of selection bias. One bias is clearly demographic as it has been noted that populations active on social media tend to be slightly younger compared to the average of the general population (Gries and Fastenau 2020, McDonald et al. 2019a). Further, some online communities might emerge as a result of specific unmet needs or experiences, so that the level of unmet need is over-represented in these communities. Finally, as activity on social media follows a power-law distribution (Muchnik et al. 2013), online communities might mainly reflect the views of extremely active users. Finally, groups without access to the internet or those with low digital literacy might be severely underrepresented. In general, user behaviour in online communities is fragmented with some users posting actively while others tend to listen to the conversation passively (Han et al. 2012). The voices of the more passive users would also be under-represented in SML in spite of users consuming social media for healthcare reasons.

Most of the studies conducted in the SML paradigm are particularly sensitive to patients' privacy. Privacy regulations and the existence of closed communities pose considerable challenges to the comprehensive collection of social media listening data. Often, the data posted and available for public viewing is not allowed to be scraped in a social media listening project, resulting in selection bias and potentially skewing results. Most published studies are carried out with content that has been made public without any further protection on the Web (e.g. Delestre-Levai et al. 2021, Farrar et al. 2021, Hswen et al. 2018) and apply methods to anonymize patients by removing or pseudo-anonymizing user names (e.g. Delestre-Levai 2021, Farrar et al. 2021, Gries and Fastenau 2020, Hswen et al. 2018, Reuter et al. 2021). While some studies have obtained explicitly approval by an ethics committee (Cook et al. 2019b, Farrar et al. 2021, Gries and Fastenau 2020), others have mentioned explicitly to be exempt of obtaining approval due to the fact that they used only data that has been explicitly and overtly made public (see e.g. Donkers et al. 2020). While it is clearly a best practice in SML to rely only on freely and publicly shared content and applying methods to ensure the non-identifiability of patients, it is an open question if this practice is sufficient to meet the privacy concerns of patients and other stakeholders. A challenge thus continues in adequately addressing privacy concerns and ethical standards (Cook et al. 2019a, McDonald et al. 2019b)

Advantages	**Challenges**
• **Identify priorities and outcomes that are important to patients** (James et al. 2020) • **First-person authenticity, fresh, spontaneous and unbiased patient perspective** (Farrar et al. 2021) in their own words (Cook et al. 2019a, Delestre-Levai et al. 2021, James et al.	• **Limited generalizability to larger population** (Delestre-Levai 2021, McDonald et al. 2019a) • **Limited access to demographic data** (Hswen et al. 2018)

2020), **unsolicited and unfiltered patient insights** • **Complement existing data sources and research instruments** (Delestre-Levai et al. 2021, Gries and Fastenau 2020, McDonald et al. 2019b) • **Holistic and more complete picture of patient experience** (Cook et al. 2019a) • **Overcome biases in the design of interviews** (Cook et al. 2019a) • **Unbiased, non-interventional data** (Gries and Fastenau 2020) • **Inform design of other research instruments** (Cook et al.2018, Gries and Fastenau 2020) • **Access to social context and emotional journey** (Delester-Leval et al. 2021, Gries and Fastenau 2020) due to greater disclosure (Farrar et al. 2021) • **Follow concepts through full patient journey** (Gries and Fastenau 2020) • **Minimize burden and requirements on patients** (Cook et al. 2019a) • **Facilitate cross-geographic analysis** (Cook et al. 2019a, Delestre-Levai et al. 2021) • **Represent perspectives of patients who are underrepresented in trials or are difficult to access** (Farrar et al. 2021) • **Address underrepresented or rare conditions** (Rocha et al., 2018) • **Access hard-to-reach populations** (Ugwudike & Sanchez-Benitez, 2022) • **Analysis of diverse and broad populations** (Moorhead et al., 2013)	• **Selection bias** (Gries and Fastenau 2020, McDonald et al. 2019a) • **Non-confirmed, self-reported diagnosis** (Mc Donald 2019a, Delestre-Levai, 2021) • **Privacy and ethical concerns** (Cook et al. 2019a, McDonald et al. 2019a) • **No possibility for following-up or clarification** (Cook et al. 2019a) • **Negative conversations may be vocalised more often than positive perceptions/experiences** (Cook et al. 2019b) • **User activity imbalance** (Han et al. 2012) • **Users' tendency to self-diagnose and potentially misdiagnose themselves**, especially in the context of mental disorders (Chochol et al., 2023)

• **Identification of Events vs Longitudinal Trends** (Cook et al. 2019b) • **Cost-effective, scalable approach** (Delestre-Levai et al. 2021) • **Data access in real-time** (Bunting et al., 2023)	

Table 2: Advantages and Challenges associated to SML as reported in the literature

In summary, SML is a widely applied methodology that has been used for a range of different indications and that has matured considerably over the last 5 years. By now, a clear convergence in terms of methods and best practices can be observed. SML has many benefits: i) it provides access to the authentic, unfiltered, unbiased and first person experience of patients, ii) it can completement effectively existing instruments by highlighting priorities and outcomes of relevance to patients, and iii) it facilitates a more holistic view of patients' needs by providing access to their social context and emotional journey, and iv) it allows to tap into the language that patients use to express the concepts that are important to them, thus potentially informing the design of follow-up instruments such as questionnaires.

From a methodological perspective, SML can overcome some of the biases inherent in methods that operate with pre-defined questions. It can further reduce the burden on patients and allow to scale patient experience research across geographies and to larger populations.

Remaining challenges include the reliance on self-reported diagnosis, limited access to demographic information, and the potentially limited generalizability to the overall population. Ensuring that privacy of patients is respected not only from a legal perspective is an important concern.

As any other method, SML has clear benefits and limitations that need to be balanced to pave the way for its wider adoption as an accepted method to capture what matters to patients. The fact that social media is an effective method to obtain the authentic and unfiltered perspective of large numbers of patients comes at the price of a reduced control about the population in terms of demographics and fulfillment of inclusion criteria. Given this trade-off, SML can effectively complement existing research instruments that are more established and controllable but might give us a limited perspective of patients' needs.

3 Patient Perspective

Patient Advocacy Groups have been increasingly emphasizing the lack of involvement of patients in research design. The International Neuroendocrine Cancer Alliance (INCA), for instance, is a global alliance made up of 20 patient advocacy groups and research groups in 17 countries from Asia, Asia Pacific, Europe and North America. In a recent survey (Leyden et al., 2020) among i) patient leaders, ii) patients and caregivers, as well as iii) healthcare professionals, INCA identified that over 32% of patient leaders believe that unmet needs of patients are not addressed sufficiently in the current standard of care. Regarding the involvement of patients in research design, 82% of patient leaders and 53% of patient and family think that patients are not sufficiently involved in research design.

Further evidence for the fact that the level of patient-centricity in drug development is regarded as low comes from the AURORA project that has carried out a large survey in order to analyze the ability of sponsors to execute on patient-centricity (AURORA Project 2018). Between July and November 2017, feedback was gathered from 1,282 participants who chose to take part in an online survey. While all participants agreed on the importance of patient-centricity (95% rated importance over 8 on a scale from 1-10), only 30% had confidence (rating of 8 or higher on a scale from 1-10) in the ability to deliver on patient-centricity. Among patients, this confidence was even lower, just 11,5% (AURORA Project 2016).

Interviews with patient leaders and representatives (Lowe et al. 2016) have highlighted that patients wish to be involved in early phases of drug development and not only towards regulatory approval. The study highlighted that patient representatives emphasized that, while not all patients can directly inform the science behind drug development, the insights they can provide around their perceptions of benefits and risks, relevance of outcomes and overall impact on daily life are invaluable and cannot be provided by any other stakeholder.

As part of the assessment of the status of FDA's PFDD initiative as carried out by the Eastern Research Group (ERG), patient representatives were also interviewed; one important conclusion was that patient representatives felt that a greater attention to psychological aspects of the disease, quality of life and measures of the ability to daily function is needed (ERG 2021).

Prevalence and uses of social media

In a consumer survey among adults in the U.S. to analyze the use of social media for healthcare-related purposes, in 2012 the PWC Health Research Institute found that 42% of consumers have used social media to access health-related consumer reviews (PWC Health Research Institute 2012): 32% have used social media to view family / friend health experiences, and 29% have sought information related to other patients' experiences with their disease. A more recent report by the Pew Research Center (Silver et al., 2019) on the use of social media by mobile phone users in emerging markets revealed that 61% of mobile users have looked up information about health and medicine for themselves and their families. In fact, in terms of information seeking activities, looking up health-related information was the top activity.

It has been found in literature studies that patients do not use social media to circumvent healthcare professionals, but rather use it as "*a complement to healthcare professional services to fulfill the needs that can not be met by HCPs"*. (Smailhodzic et al. 2016). One of the crucial reasons for patients to seek support online is their dissatisfaction with professionals' inability to meet their emotional and informational needs. The strive for social support by other patients is thus one of the main reasons for social media use by patients (Smailhodzic et al. 2016). Smalhodzic et al. have identified the specific types of social support that are seeked by patients:

- *Emotional support:* referring to support gained through expressions of care and concern
- *Esteem support:* referring to communication that fosters patients' self-esteem or belief in their ability to handle problems
- *Information support:* referring to communication that provides needed information
- *Network support:* communication that affirms patients' belonging to a network or reminds them of support available in their network

Most importantly, sharing health-related experiences in online communities has an effect of empowerment on patients, increasing their subjective well-being, psychological well-being and leading to increased self-management and control (Smailhodzic et al. 2016).

When engaging with social media, users are willing to disclose very intimate information (Suler 2004). In fact, it has been shown that the anonymity of many social media sites increases the level of self-disclosure (Ma et al. 2016). The most important barriers and problems related to social media use for healthcare purposes are thus privacy issues and issues related to the unreliability of social media (Antheunis et al. 2013). In spite of the high sensitivity to privacy, the consumer survey by PWC (PWC Health Research Institute 2012) has shown that more than 30% of respondents would be comfortable having their social media conversations monitored if that data could help identify ways to improve their health. In a study with adults presenting to an academic, urban emergency department, Padrez et al. (2016) found out that out of those patients having a social media profile, 71% consented to share their social media data to compare it to their Electronic Medical Records (EMRs). A survey on health topics carried out by Pew (Fox, 2011) corroborates this willingness to share data. In spite of reservations, approximately 70% with a medical condition believe data could potentially be used without their knowledge to deny them healthcare benefits or to deny them job opportunities. More than 90% of interviewees would share their health data if it helps to improve are or supports research and approximately 80% would share information with drug companies if it contributes to learn more about the disease or make safer products. These figures convey that a significant share of patients are willing to share their social media data for research purposes if it contributes to improving their condition and those of their peers.

Taking stock, social media has an important function for patients, providing informational, emotional and social support to them. The anonymity of social media provides a safe environment in which patients are willing to disclose very sensitive and private experiences.

Patients and patient leaders / advocacy groups have emphasized the fact that there are significant unmet needs and demand a higher involvement of patients in research design and evidence generation activities. While privacy is an important barrier, a significant share of patients are willing to share their anonymized data publicly if it has the potential to improve their condition.

Overall, social media has the potential of reducing burden and making patients more “involved” in drug development by sharing valuable experiences that can guide development, clinical trial design etc.. An open question is certainly if social media is, from the patient perspective, a legitimate and ethical method to capture their needs, preferences and priorities.

4 Industry Perspective

Pharmaceutical companies strive to develop innovative treatments for different needs and under various biological, technological, medical, economic and social constraints. At the end of the drug development process lies the decision of patients, or their caregivers, to accept a treatment that may improve their condition. This decision is based on information, sometimes conflicting (Elstad, 2012), available to them and a set of considerations and trade-offs involving aspects such as affordability, trust (Cuevas et al., 2019), involvement in the decision (Shay & Lafata, 2015), risk perception (Bonner et al., 2021), convenience, expected or perceived benefits and adverse effects. After a lengthy and costly drug development process, it is at that point that patients may express their views in a most direct manner, either by actively engaging with the treatment or by resorting to rejection or

non-compliance. Thus, treatments that have been successful in clinical trials may not find the expected success in patient uptake (Matikainen et al., 2015).

One reason for this is that, despite progress in shared medical decision-making, patients have had limited opportunities to express their opinions on their disease and treatments in a way that directly affects the pharmaceutical development process. Clinicians and doctors have historically played a gatekeeping role by interfacing directly with patients and translating these interactions into a view of the patients' needs, including clinical rating scales, disease conceptual models and treatment and diagnostic guidelines. This gatekeeping role has also influenced the definition and evaluation of what clinical success means, ultimately steering pharmaceutical companies away from a full understanding of the patients' view and towards a clinician's view of the disease (Morel et al. 2017, Postmus et al. 2016).

Patients and their caregivers, however, base their treatment decisions on a multi-factorial set of elements that go beyond strictly medical considerations. For pharmaceutical companies to create treatments that are relevant to patients, and that are created in a way that is most considerate to them, it is crucial to understand the gap that patients perceive between what they need and what is being offered to them. Thus, it is possible to talk about a "translational gap" between clinical models of patients and actual patients being treated while being busy with their daily lives.

The patient's view can, in fact, help influence drug development even at the earliest stages, in a way that increases the chances that a medicine will be successful with patients in real-world settings. For instance, lack of progress in some disease areas could be ascribed to the selection of the wrong population, or of inadequate endpoints, in clinical trials ("Probably the easiest way to ruin a clinical trial is to choose the wrong endpoint." (Kellum et al., 2017)). The right choice of population or endpoint could result in avoiding pseudo innovation, in which therapies do not address the most pressing needs of patients. A more exact understanding of patient populations and potential clinical endpoints could also lead to better target product profiles (TPPs), which define the desired characteristics of the treatment that a pharmaceutical company is aiming to develop.

To partially address such issues there has been a growing emphasis in measuring quality of life (QoL) outcomes in clinical trials, which can be captured through patient-reported outcomes (PROs) (Fayers et al. 2013, Lohr & Zebrack 2009). PROs are patient self-reports that aim to capture the opinion of patients in ways that can be systematically evaluated and can be used to, among other things, identify changes in disease treatment that lead to the largest improvement in QoL.

In general, PROs can have shortcomings, such as response bias and lack of content validity (Chang 2019). Moreover, there is a set of specific challenges for PROs used in clinical trials. First, clinical trials do not reflect the real-world conditions in which patients decide and experience their treatments. Second, PROs used in clinical trials can be constrained by past practice because validated and widely-accepted PROs are necessarily long-established, and perhaps outdated given fast social and technological changes. Additionally, many PROs have been created with limited patient input, such as with the aid of patient organizations or a limited set of patient interviews, which may not completely reflect the target population of the trial and treatment. Finally, PROs in clinical trials are not used to understand all patients of a disease, but only those patients who qualify and enroll in the trial.

A complementary approach to understanding the patient's view is the analysis of social media conversations and posts created by patients online. This content made of patients' unfiltered opinions

about their real-world experience represents an opportunity for pharmaceutical companies to better understand the patients' view about many aspects of their disease and treatments, as well as related social determinants of health. While the usefulness of listening to health-related social media can appear intuitive to anyone who has used social media for health reasons, the regulatory uncertainty surrounding it has deterred pharmaceutical companies from widely adopting its use. Thus, while patients have been using the internet since its inception to discuss their health condition, and this usage exploded along with social media channels such as forums, blogs and microblogs (Moorhead et al., 2013), only increased clarity in the regulatory framework together with encouragement from regulatory agencies have fostered the research of SML by pharmaceutical companies (see Figure 2). Thus, despite the benefits of SML, legal and regulatory clarity are necessary stepping stones in furthering its adoption.

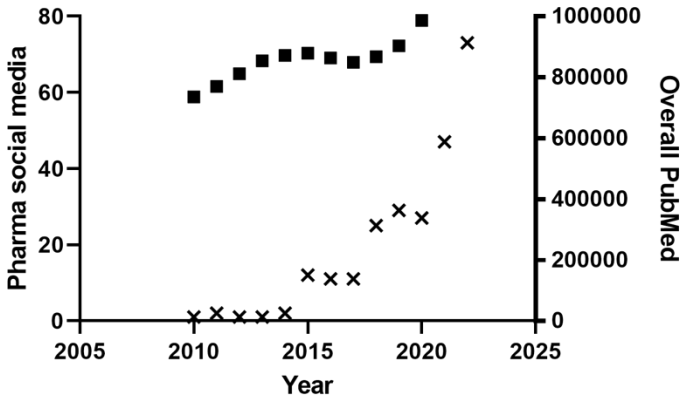

Figure 2. Number of publications listed in PubMed with a large pharma affiliation and mentioning "social media" per year (crosses in the Figure and numbers on the left axis) and overall number of publications listed in PubMed per year (blocks in Figure and numbers on right axis).

Another factor to consider beyond legal clarity is variability in the laws and their implementation across countries, which requires establishing interpretations and best practices that apply to multiple jurisdictions, and that address legal uncertainties, particularly given the global nature of online content and geographic dispersion of multinational companies.

In the EU, the General Data Protection Regulation (GDPR) established a generally more restrictive legal framework for SML that is being increasingly taken as a reference by legislation in non-EU countries. The GDPR seeks to balance legitimate interests for data use with the fundamental rights and freedoms of individuals, as well as their expectations. The GDPR also introduces certain exemptions for scientific research purposes that support a broader use of SML, including, if scientifically justified, inferring patient information not explicitly stated or cross-integrating patient data from different platforms. To qualify for this research exemption the following conditions would need to apply (EDPS 2020): (1) relevant sectoral standards of methodology and ethics are followed, and (2) the research is carried out with the aim of growing society's collective knowledge and wellbeing, as opposed to serving primarily private interests. Thus, legal and ethical standards are not independent from each other. The GDPR includes, in any event, regulations in terms of data storage and processing that also apply to research activities (Kotsios et al., 2019, van Veen 2018).

US legal practice, both at the federal and state level, is, thus far, generally less restrictive than the GDPR. Thus, following the principle of the "most restrictive rule," GDPR principles, including country-specific implementations, should generally apply to SML at the moment, with the exclusion of activities fully circumscribed to a country, which may be tailored to local laws (e.g. Chinese-internal SML).

That said, US federal regulation is relevant as one could consider some types of SML as observational research, which are research activities that may not involve any interaction with the study participants. It is unclear which SML activities performed by a pharmaceutical company to understand patients, or caregivers, better could fall outside of this regulatory umbrella.

Based on US regulatory practice, if the observational research activity only involves "observation of public information" (Moreno et al. 2013) it may not require Institutional Review Board (IRB) approval nor patient consent. It has been debated whether open social media sites that require user authentication can still be considered public. In such cases, the expectation of the users and the terms and conditions of the site may help determine this. A simpler, but more restrictive, approach is to automatically disregard any site which requires login to avoid any potential conflicts (Gonzalez-Hernandez, 2019). This approach could also apply when considering whether online content is "manifestly made public," which is a precondition established by the GDPR in some cases for the processing of certain types of sensitive data.

Another legal aspect concerns the terms and conditions for each social media site, which determine the range of activities that are allowed with the site's content. Terms and conditions vary widely across sites and can be unclear about data availability for reuse. Thus, sites can range from early-internet-style communities in which there is no explicit restriction in data reuse, to sites from for-profit companies geared to the reselling of user data, which many of the users may have failed to notice. Indeed, many users might find it difficult to judge a site's terms and conditions, whether because these are difficult to locate in the first place, or because of their length and complexity. Thus, there is a contrast between the care by which terms and conditions need to be considered by those performing SML and the lack of attention to them paid by many of the users who contribute the content. When working with companies managing these sites, reviewing the legal and ethical aspects of their work should be, therefore, considered as an integral part of the process. Additionally, since terms of conditions can change over time, best practice would be to keep records of them at the time that social media activities were performed.

Beyond grappling with legal aspects, pharmaceutical companies need to address ethical questions, which can be of different urgency across countries and cultures. While the ethnography of online communities is an established field of academic research (Tunçalp & Le, 2014), patients have diverging opinions about its appropriateness and this opinion can be highly context-dependent (Fiesler & Proferes 2018, Golder et al., 2017). Thus, when it comes to research with the goal of improving healthcare, opinions can be more supportive (Bond et al. 2013, Hemphill et al. 2022). Despite that, there could be additional concerns when the research is done by pharmaceutical companies. Patients can argue that their trust has been betrayed because their online postings, even if posted on open sites with no password protection, were not meant to benefit for-profit corporations or could be misused for marketing and sales purposes.

Such ethical considerations could be approached within the ethical framework of observational studies. It has been argued over whether observational studies, which are widely performed in healthcare research, can be ethical without patient consent, which is the bedrock of modern clinical

practice (Bazzno et al. 2021). Thus, for example, the Economic and Social Research Council (ESRC) from the UK considers ethical the forgoing of patient consent as long as a study is not ”undertaken lightly or routinely. It is only justified if important issues are being addressed and if matters of social significance which cannot be uncovered in other ways are likely to be discovered” (ESRC 2010). It could be argued that SML can fulfill those requirements, with some important caveats. First, that it is not “undertaken lightly or routinely.” Continuous mining of social media sources would not fall within the scope sanctioned by the ESRC. Second, that it has a focus on matters of social significance, such as improving the healthcare of patients, which may not apply to certain sales or marketing questions. Finally, that alternative methods are insufficient.

Additionally, the ESRC justifies forgoing the requirement of informed consent when “overt observation might alter the phenomenon being studied” (ESRC 2010). Indeed, the feasibility of obtaining informed consent in SML would hinge on the ability of communicating with the patients, or caregivers, who post online, which might be unfeasible. Additionally, the act of contacting users may bias their own future online actions as well as those of their peers, as they may start behaving differently, especially if they have a negative pre-established view about pharmaceutical companies. Therefore, contacting users to notify them of listening activities could change the nature of online conversations in a way that could be detrimental to future SML activities by any research entity, whether pharmaceutical or not.

A broader review of ethical recommendations (Ford et al., 2021) suggests that SML for health research can be ethical without informed consent when there is an emphasis on ensuring user anonymity, minimization of possible harms to users, a focus on public benefit, transparency in data access and analysis methods, and abidance to the law and terms and conditions from the source sites. Beyond these considerations, there could be additional ethical aspects if the research is being performed by for-profit corporations such as pharmaceutical companies, which could lead to the demand that patients should receive a benefit from sharing their data online. While payments for participation in research studies are considered acceptable to compensate for study burdens and out-of-pocket expenses, or to attract participation (Gelinas et al. 2018), there is also a question of fairness in the sharing of economic benefits that may not otherwise arise in not-for-profit research. This question could be started to be addressed if the economic benefits derived from insights from SML could be quantified.

It could also be argued that pharmaceutical companies that do not try to understand patients using data that is freely available (or, in the GDPR parlance, “manifestly made public”) are performing a disservice to patients. Patients would like their treatment to be based on all the information available and failing to analyze these data to improve the way healthcare is performed could be considered an ethical error of omission. That said, there does not seem to exist a moral or legal imperative in the field of medicine to “know everything.” The principles of medical neglect, for example, use as their reference the following of established medical practice. The Hippocratic oath, to give another example, is based on acting according to the “greatest ability and judgment.” The main ethical underpinning for SML could be, instead, the necessity to proactively listen to the people who bear, or will bear, the consequences, positive and negative, of treatments being developed for them.

In fact, there is already a legal mandate by which pharmaceutical companies have the duty of actively “listening,” in particular to collect information linked to adverse events of the drugs they market (EMA 2015, EMA 2017). In these activities, known as pharmacovigilance, social media is acknowledged as a source of relevant patient data that can play a complementary role to existing approaches (Convertino et al. 2018, van Stekelenborg 2019). Expanding the analysis of these same

social media data beyond pharmacovigilance to aspects of QoL, and beyond, would be an acknowledgement of the importance that these areas have to patients, and which may not be inferior to that of pharmacovigilance. Thus, actively evaluating information from patients about drug-related information as expressed in social media channels could be considered a pursuit of similar ethical importance as pharmacovigilance activities.

5 Considerations by regulatory authorities

Regulatory authorities worldwide have embraced the challenge of adapting their frameworks to ensure that patients' needs and preferences are systematically taken into account into drug development. The US Food & Drug Administration (FDA) for instance has defined Patient-focused drug development (PFDD) as a *"systematic approach to help ensure that patients' experiences, cultural traditions, perspectives, needs, concerns and priorities are captured and meaningfully incorporated into drug development and evaluation.*" The main goal of this initiative is to contribute to improved health outcomes for different groups of patients.

In this section, we discuss briefly the position of different regulators on the systematic involvement of patients in drug development and discuss specifically the views on how social media patient listening approaches can support and complement existing regulatory decision making practices. We finally raise important questions that need to be clarified regarding the role and impact that social media can have on regulatory decision making.

5.1 Patient-focussed drug development initiatives

5.1.1 FDA Considerations

The US Food & Drug Administration (FDA) has so far played a pioneering role in the PFDD initiative, being the first regulatory body having published guidelines on how patient experience can be incorporated into drug development. As a consequence of the 21st Century Cures Act of 2016 and the FDA Reauthorization Act of 2017, the agency has issued a series of guidelines for industry and stakeholders providing recommendations on how patient experience data could be incorporated into PFDD:

- **Collecting Comprehensive and Representative Input** (FDA 2020, Final Guidance available as of June 2020)
- **Methods to Identify What Is Important to Patients** (FDA 2022b, Final Guidance available as of February 2022)
- **Selecting, Developing or Modifying Fit-for-Purpose Clinical Outcomes Assessments** (FDA 2022c, Draft Guidance available since June 2022)
- **Incorporating Clinical Outcome Assessments into Endpoints for Regulatory Decision Making** (FDA 2023, Draft Guidance available since April 2023)

In accordance with the Cures Act, the FDA has conducted assessments of its use of patient experience data in 2021 and follow-up assessments are planned for 2026 and 2031. The 1st assessment has been carried out in cooperation with ERG and documented correspondingly (ERG 2021). The assessment has emphasized that there is still significant uncertainty regarding how exactly the FDA might use patient experience data and it is frequently emphasized that the FDA and

industry are currently *"in the middle of a learning curve"* ahead of understanding and developing best practices. When the FDA uses patient experience data in regulatory decision making, it usually takes the form of considering PROs and other COAs as primary endpoints in the benefit-risk analysis for a marketing application as well as as background context for the review.

For drug and biologic marketing applications received after June 12, 2017, the FDA has been fulfilling the requirement to make a public statement about its use of patient experience data by including a Patient Experience Data Table in review documents for approved applications. As of June 2017, the FDA is required to publish a brief statement about how patient experience data that was part of a drug biologic application was used as part of the review. From all NME NDA / BLA reviews that mention patient experience data, at the time of writing 88% contain such a Patient Experience Data Table. In its review, FDA may use patient experience data in a variety of ways:

- Summary of Data: meaning that Patient Experience Data is acknowledged in the summary of data and evidence available
- Interpretation of Data: meaning that Patient Experience Data is used as context to support the interpretation of data
- Analysis of Data: meaning that Patient Experience Data is actually used to enhance the analysis
- Factor in Decision: meaning that Patient Experience played a decisive role in the final decision

Among the best practices regarding the use of patient experience data for PFDD, the following have been identified (ERG 2021):

- Early and frequent communication between FDA and applicants
- Development of a solid data analysis plan
- Applicant use of patient experience data to help design clinical trials
- FDA to use patient experience data to frame the review
- Sharing of patient experience data with the patient community

It has been stated in general that applicants need more clarity and guidance on how patient experience data can be used as background/context as well as for benefit / risk analysis.

5.1.2 EMA Considerations

In their strategic reflection paper "EMA Regulatory Science to 2025", the EMA has generally stressed the importance of patient involvement in drug development. As part of the goal 2 on *"Driving collaborative evidence generation - improving the scientific quality of evaluations"*, the importance of including patient preferences to inform benefit-risk assessment has been emphasized, as well as the identification of areas of high unmet need. The paper emphasizes in general that *"patient perspectives are particularly important, and their involvement can greatly improve trial design and conduct, and the usefulness of the results and medicines developed"*. A goal is thus to foster the input of patients / patient representatives and carers in the regulatory process. As part of

goal 3 on *"Advancing patient-centered access to medicines in partnership with healthcare systems"*, the EMA has stressed that it is looking to enhance its methodological portfolio to enable greater input from the wider patient community in a systematic manner. It has mentioned in particular the aim to *"explore and deploy additional methodologies to collect and use of patient data for benefit-risk assessment"*. It has highlighted in particular that new digital technologies have the potential of providing a more holistic view of the patient and the disease and that "*If analysed appropriately, these new sources of data can create new evidence which has the potential to add significantly to the way the benefit-risk of medicinal product is assesses over their entire lifecycle"*.

In a recent joint reflection paper of the European Medicine Agency (EMA) and the International Committee for Harmonisation (ICH), the agencies have stressed that *"it is increasingly critical to develop a harmonized approach to collecting and incorporating patient perspective for these to become more prominent in drug development and decision making"* (ICH 2021). The authors have emphasized that to maximize benefit of patient perspectives in these areas, regulators and drug sponsors need to employ methods and measures that:

- Include patients and caregivers as partners to best inform the work
- Ensure the information collected is sufficiently reliable, valid and representative to be used as basis for planning and decision making
- Can be deployed in a timely and sustainable way
- Will be relevant to patients and their caregivers
- Account for heterogeneity of groups

In line with the FDA, the EMA / ICH has highlighted the importance of identifying important impacts and concepts from patients as a basis to select, modify or develop clinical outcome assessments that can demonstrate meaningful change in patients' lives. The EMA / ICH specifically lists the questions that could be answered from the patients' perspective:

- What disease burdens and treatment effets matter most to patients that might be addressed by a medical theory?
- What would be the best way to measure these disease or treatment burdens / effects in a clinical trial, and are the methods acceptable for patients?
- What would be the most appropriate endpoints to use in clinical trials (and robust enough to inform regulatory decision making)?
- What are clinically meaningful changes in an endpoint from a patient perspective?

As an interim conclusion, it can be stated that the main use case for patient experience data is to inform the definition, development and validation of Patient-Reported Outcomes (PROs) and other types of Clinical Outcome Assessment. It has been particularly noted that patient experience data can play a role in *"providing supporting information in situations where the condition is not well characterized, as with some rare diseases"* (ERG 2021).

5.1.3 MHRA Considerations

The Medicines & Healthcare products Regulatory Agency (MHRA) has also emphasized the importance of the inclusion of patient perspectives in drug development in their strategy paper on *"Saving and Improving Lives: The Future of UK Clinical Research Discovery"*. One of the five pillars of the MHRA vision for UK clinical research delivery is patient-centered research. The MHRA has acknowledged that *"patients must be routinely involved in the design of clinical research to ensure outcomes match their needs and studies are designed with real participants and the realities of their daily lives in mind"*. As a first step in this direction, the MHRA has started a pilot in March 2021 to support the strategic goal of integrating the perspective of patients into the decision making process regarding the approval of new medicines. As part of this pilot, applicants will be specifically requested to provide evidence on the patient involvement activities undertaken when developing their product. The main goal for MHRA is to learn from the evidence submitted to define their strategy.

5.2 Social media patient listening in PFDD

Social media research has been identified as a potential method for generating experience data in the various guideline documents on PFDD issued by FDA. In their guidelines, FDA has recommended that patient experiences are captured as directly reported by patients rather than through mediation or interpretation of others.

SML satisfies this requirement of capturing the direct input of patients and in this sense is comparable to interviews carried out directly with the patient (1-on-1, deep or cognitive interviews, concept elicitation interviews etc.). Social media patient listening differs from these more established instruments in that the instrument is not "designed" in the sense of defining a set of questions to ask to the patients. Rather, social media patient listening captures the spontaneous and unsolicited input of patients as shared by users while being active on social media. By not requiring to define questions a priori, social media patient listening does not suffer from common biases inherent in the design of a questionnaire (leading questions, bias due to order of questions etc.).

While 1-on-1 interviews and focus group studies are carried out with between 5 and 20 participants, SML has the advantage of capturing the perspective of a more diverse and broad patient population. It can thus contribute to the representativeness of patient experience data across the full diversity of the patient population and would help to fulfill recent draft FDA guidance requirement to provide "Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials" (FDA 2022a).

The benefits of social media patient listening recognized by the FDA are the following:

- May allow access to hard-to-reach populations
- Cost and time efficient
- Easy to implement
- Accurate and automatic capture of data
- Low burden on participants

In general, social media patient listening should not stand on its own, but complement existing methods such as one-on-one interviews or focus group studies or other survey data. The FDA has mentioned mixed method designs that allow different research instruments to be applied in a synergistic manner, thus complementing each other. We spell out below how social media patient listening fits into the envisioned synergetic use of different methods identified by the FDA:

- Harmonizing and confirming results from different methods
- Supplementing and clarifying results from one method with results from another method
- Using results from one method to inform the design of another method
- Discovering inconsistencies, contradictions and new perspectives, and reframing of questions or results from one method with questions or results from the other method
- Expanding the scope (range) of research questions by using different methods for different components of the research question (expansion)

In general, the FDA explicitly has refrained from giving precise methodological indications on how exactly different methods should be used or combined, stressing consistently that methods and data will be assessed from the perspective of whether they are fit for purpose to address and answer the research question at stake. In the context of using social media to support we see the following potential impact points or use cases that need to be spelled out in more detail to provide clearer guidance on how social media derived guidance can impact regulatory decision making:

- Social media as background on the impact of the disease on patients (natural history of disease)
- Social media to establish an `unmet need'
- Social media as a way to define and demonstrate relevance of an endpoint
- Social media as a way to inform the assessment of the benefit-risk tradeoff

Summarizing the regulatory considerations, it is fair to say that regulators acknowledge the need for new methods and techniques to reliably capture the experiences of patients and what is important to them. The FDA in particular has highlighted that social media could complement more established qualitative and quantitative research methods by reliably capturing patient insights while minimizing their burden. The key methodological challenges are inaccuracies, reliance on patients' self-disclosure, missing data, privacy protection. The main benefits seen by regulators are: i) enhanced access to hard-to-reach populations, ii) cost and time efficiency, iii) ease of implementation, iv) low burden for participants, and v) access to the direct and unmediated voice of the patient. From a methodological perspective, ensuring the generalizability to the target population while minimizing biases to particular segments of the population is a key challenge seen by regulatory bodies. Understanding how exactly social media patient listening can complement existing research instruments beyond the current general statements made by FDA is an important priority.

6 Synthesis

Patients are often concerned that research and development for new medicines is disconnected from their needs and priorities. Indeed, there is an increasing recognition that involving patients in medicines research and development can provide significant value to all stakeholders involved. Patients have a unique perspective on what it means to live with a particular condition, and this perspective can be invaluable in drug development. Patients can provide insights into the impact of a particular condition on their daily lives, including symptoms, quality of life, and the practical challenges they face, and may also help to design, improve recruitment and retention in clinical trials.

An important question certainly is how to include the perspectives of patients in a manner that is effective, efficient, reduces the burden of patients and ensures that their perspectives are accurately taken into account, while the approach for doing so is legitimate and faithfully captures the perspectives of patients. There are two important considerations here. For one, Haerry et al. (2018) have discussed that what is important is to include the naive and "lay perspective" of patients in the process as the beneficiaries of drug development, as they are the only ones that from their lay perspective understand which improvements are needed, without necessarily having to understand the methodological, scientific, regulatory and practical aspects involved in bringing these improvements about. It is exactly this "lay perspective" that is mostly relevant for drug development. Haerry et al. (2018) have highlighted a paradox in that the more patients are involved in the process and the more educated they get as part of this engagement, the less they represent a naive and lay perspective. For another, it is key to minimize the burden of patients associated with their involvement in drug development, which is considerable in the case of relying on PRO instruments (Bodart et al. 2019).

Social media serves an important function for patients providing informational, emotional and social support and a conducive environment for patients to disclose sensitive and private experiences through anonymity. Within this anonymity, they are willing to share important information about their disease, how it impacts their lives, the challenges they face and which unmet needs still exist. Thus, listening to patients on social media offers an immense opportunity to gain access to the authentic, unfiltered, unbiased and first-person experience of patients in addition to providing a more holistic view of patients by highlighting their social, cultural and emotional contexts. It is thus providing us access to what Haerry et al. (2018) have called the "lay perspective" of patients, while minimizing the burden for them to be involved in drug development.

A thorough understanding of patient experiences and priorities is key to narrowing down the gap that exists between the treatments on the market and under development, and the actual needs of patients and the outcomes that would have a significant positive impact on their lives.

Sponsors are clearly embracing the challenge of developing treatments that are relevant to patients and have so far been very active in exploring the potential of social media to learn about patients' needs, as this article, and the systematic review carried out within it, clearly corroborate. Methodologies for analyzing the perspective of patients from social media are mature, and a clear convergence in terms of data protection practices can be observed. Best practices exist that allow to carry out patient SML studies in a way that preserves anonymity to ensure protecting patients' privacy rights and relies on content that has been made manifestly public. SML can be carried out in a way that is ethical even without explicit consent if it is done for research purposes, not conducted routinely, and if the insights have a positive societal impact and can not be gained or uncovered easily in other ways. Developing new treatments that alleviate the burdens of patients is without doubt of high societal interest, so that one could argue if there is not even a clear obligation to listen to patients' voices on social media.

Regulatory authorities have consistently highlighted the importance of inclusion of patient perspectives in drug development in order to maximize real-world outcomes that positively impact patients' lives. While EMA and MHRA are clearly committed and even mandated to include patient perspectives in drug development, the FDA has even provided a set of regulatory guidance documents to specify their methodological expectations on how patients should be included in drug development.he EMA has clearly stressed that "new technologies" should be explored and the FDA has explicitly included social media listening as one of the important methods to capture patient experience data. Yet, the FDA has also stressed that as far as the use of social media is concerned, we are all part of a learning curve. The main issue at stake is to understand how representative the perspectives are and how generalizable they are to the actual target populations. In general, we need to understand and balance the methodological tradeoffs between the benefits and drawbacks of relying on social media. At the one end of the spectrum, online populations might be biased to certain segments of the patient population, data collection might be affected by selection bias and might be incomplete as patients would not spontaneously provide information on all aspects relevant for a certain question. Furthermore, information on social media cannot be verified. In this sense, the reliability of social media is not comparable to data rigorously collected in HRQoL studies or PRO studies, but it could certainly complement or inform the design of such instruments and make sure that important aspects are captured, contributing to ensuring content validity. On the other side, social media listening has the potential to access large numbers of patients, even for rare conditions, can ensure that we get the real, undistorted voice of patients, can ensure that we capture what is relevant from their perspective and minimizes the burden of collecting patient experience data. Future activities should be devoted to developing methodological approaches and best practices that balance the above mentioned drawbacks and benefits. Regulators have stressed that their ability to provide regulatory guidance is limited and that they will accept any method that is fit for purpose. It is thus in the hands and responsibility of the community of sponsors, tech vendors and patient organizations to define methods that are fit for purpose in dialog with the regulators.

Overall, the interests of the three stakeholder groups that we have discussed in this article are clearly aligned. Patients want to have a stake in drug development and their voices to be considered from early on. Social media is a way to do so while minimizing their burden. Sponsors have already invested in developing methodologies to capture the online patient experience as it gives them access to the first hand and direct experience of patients and is a cost effective and scalable method to incorporate their perspective into drug development. Regulatory bodies are explicitly acknowledging social media as an important source of patient experience data. What is missing is a regulatory framework and policies that create certainty on how patient experience data collected from social media can be used in ways that are aligned and compliant with the interest and requirements of the three groups discussed here.

7 Recommendations

Patients, regulatory bodies and industry need to work collaboratively to accelerate patient focused drug development. From the perspective of all stakeholders, legitimacy, privacy and compliance as well methodological robustness seem to be important factors. These open points define a clear roadmap ahead that the above stakeholders can work on together to reduce regulatory, legal and methodological uncertainty in ensuring that social media patient listening can find its appropriate

place in the current methodological landscape to collect patient experience data and ensure that perspectives of patients are captured in drug development from early on to reduce the gap between what is measured in current clinical trials and what would really make a difference to the daily living and functioning of patients.

In order to leverage social media patient listening methods as a source of patient experience data to support patient-focused drug development, clearer regulations, best practices and guidelines are needed that reduce uncertainty for all stakeholders interested in leveraging social media. We see in particular the need to more specific guidelines and best practices on the following issues:

1. **Data collection:** Recommendations and guidelines are needed on how to collect data from social media in a way that is compliant with established data protection regulation (GDPR in particular) and current ethical judgements. This includes recommendations on how to collect data to minimize selection biases.

2. **Data analysis:** Standardized and robust methods are needed to generate results that generalize to the target population including measures to convincingly demonstrate robustness of analyses and highlighting potential selection biases transparent. This includes recommendations on what level of proof is required to assume that a patient with a self-disclosed diagnosis fulfills the inclusion criteria.

3. **Justification of the legitimacy and validity** of using SML to capture patient insights from the perspective of patient representatives, patient advocacy groups etc.

4. Accepted methods for using social media data to **inform the design of PRO, HRQoL surveys, interviews, questionnaires etc.**

5. Guidelines and best practices on how results from social media analysis can **enhance or support decision making on which endpoints** to include in a clinical trial.

6. Guidelines and best practices on how results from social media analysis can **support benefit-risk analysis** as part of regulatory approval.

As part of their agenda, the Expert Community Group “Exploiting Real-World Data From Social Media in Patient-Focused Drug Development Community” of the Pistoia Alliance intends to work on these topics to contribute to methodological clarification and contribute to the development of best practices, provide corresponding deliverables in the coming 18 months.

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