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ORIGINAL PAPER

Towards regulatory endorsement of drug development tools to promote the application of model-informed drug development in Duchenne muscular dystrophy

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Abstract

Drug development for rare diseases is challenged by small populations and limited data. This makes development of clinical trial protocols difficult and contributes to the uncertainty around whether or not a potential therapy is efficacious. The use of data standards to aggregate data from multiple sources, and the use of such integrated databases to develop statistical models can inform protocol development and reduce the risks in developing new therapies. Achieving regulatory endorsement of such models through defined pathways at the US Food and Drug Administration and European Medicines Authority allows such tools to be used by the drug development community for defined contexts of use without further need for discussion of the underlying model(s). The Duchenne Regulatory Science Consortium (D-RSC) has brought together multiple stakeholders to develop a clinical trial simulation tool for Duchenne muscular dystrophy using such an approach. Here we describe the work of D-RSC as an example of how such an approach may be effective at reducing uncertainty in drug development for rare diseases, and thus bringing effective therapies to patients faster.

Keywords Rare diseases · Duchenne muscular dystrophy consortium (D-RSC) · Model-informed drug development · Drug development tools · Regulatory endorsement

Abbreviations

BIV	Between-individual variability
BMI	Body mass index
BSV	Between-study variability
CDISC	Clinical data interchange standards consortium
CHMP	Committee for medicinal products for human use

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CINRG	Cooperative international neuromuscular research group
DMD	Duchenne muscular dystrophy
D-RSC	Duchenne regulatory science consortium
EMA	European Medicines Authority
FDA	Food and Drug Administration
FFP	Fit-for-purpose
LOI	Letter of intent
MID3	Model-informed drug discovery and development
QNM	Qualification of novel methodologies
RV	Residual variability
SAWP	Scientific advice working party
TAUG	Therapeutic area user guide

Introduction

Quantitative approaches (i.e., model-informed drug discovery and development, MID3) have been used to efficiently and effectively inform decision-making in drug discovery and development and reduce the costs of drug development overall. The use of models to inform drug development is considered so important, it is listed as one of ten enhancements to drug development in Prescription Drug User Fee VI [1]. Models that integrate information from disease, drug and trial features can be converted into drug development tools that can help design more informative clinical trials through inference and generation of new knowledge (e.g., clinical trial simulators). Clinical trial simulations enable researchers to evaluate and optimize design characteristics (e.g., trial size, duration and inclusion/exclusion criteria, choice of endpoints) *in silico*, prior to execution in the target patient population. Quantitative models can inform (a) how clinical endpoints change with disease progression in different subpopulations and disease stages, allowing drug developers to improve clinical trial protocols to reach more definitive conclusions on the efficacy of proposed interventions; (b) how to prospectively select subgroups of patients with a higher likelihood of responding to treatment in a shorter timeframe, or who are likely to show a larger change in the selected outcome than the overall patient population; and (c) which endpoints might show sensitivity across different stages of the disease continuum. This information would allow the design of more efficient trials to reach more definitive conclusions, while enrolling fewer patients and/or being shorter in duration. Selection of appropriate endpoints that show change in different populations of patients may also allow a wider range of patients to participate in clinical trials, and hence, reduce recruitment time. Thus, the use of clinical trial simulators ultimately benefits patients (through more informative trials that will have a higher likelihood of demonstrating efficacy of efficacious drugs), the research community (through better understanding of how disease progresses and the factors that affect progression rates), and drug developers (through more cost-effective trial designs).

Clinical trial simulations based on a quantitative understanding of disease progression in integrated patient-level datasets (as opposed to meta-data only) are particularly impactful in designing clinical trials that evaluate therapeutic interventions for slow-progressing diseases, diseases where the magnitude of change is variable, and diseases where little data is available [2–7]. Many rare diseases, defined as diseases where few patients have the condition—fewer than 200 000 patients (United States definition in the Orphan Drug Act), or fewer than 1 in 2000 people (European Union definition [8])—fit these criteria. Diseases that progress slowly or variably may require trials of longer duration to detect cessation or slowing of progression. In such trials, the change from baseline in a clinical outcome that reflects a disease symptom or sign can be attributed to (a) an efficacious treatment, if an improvement is observed, (b) a placebo effect, if the endpoint returns to its original course after an initial improvement, (c) disease worsening or (d) natural variability in the outcome measure. Patient-specific factors that may be associated with (but are not necessarily causative of) differences in progression rate occur simultaneously with, and contribute to, the effects of treatment, placebo and disease progression. Hence, clinical trial simulations must account for the interplay of disease, drug and trial (e.g., placebo) components, and their relationship with patient characteristics (e.g., demographics, genetics). The basis of these simulations are quantitative disease-drug-trial models [9], which provide a framework for understanding the extent to which each component influences the various disease outcomes.

Development of robust and broadly applicable quantitative disease-drug-trial models requires the integration of data from multiple sources. Interventional clinical trial data is useful in providing information on the effects of (a) drug, (b) trial components (e.g., placebo, dropout, study site), and (c) a mixture of disease pathophysiology and placebo. Data from observational studies (e.g., natural history studies or registries), when combined with those from interventional clinical studies, may help differentiate the extent to which the disease, placebo, and standard-of-care drugs affect the progression of the clinical outcome over time. Data collected from clinical practice or in the "real world" might also help inform disease-drug-trial models, albeit with the caveat that data must be collected in a

rigorous manner (consistent and standardized measurements), potential confounders must be accounted for, and patients must give consent for their data to be used for such purposes.

The need to integrate clinical data from relevant sources is of specific importance in the context of rare diseases. No therapy exists for many rare diseases and, therefore, most patients may not be treated regularly by specialists or attend specialty centers, meaning that little data has been collected on their condition. Furthermore, for most rare diseases, few or no clinical trials have been conducted, and those that have been are small and may be underpowered. Natural history studies are similarly small and unusual, and resources to support such studies are very limited. The consequent lack of understanding of the natural history for many rare diseases makes it challenging to understand if a potential new therapy may be effective. Moreover, in many rare diseases, gold-standard clinical endpoints or biomarkers may not have been accepted by the community, so different datasets may contain different measurements. Data supporting each proposed endpoint or biomarker is limited, and how these measurements are associated with disease progression is not definitive. Although the above challenges are daunting, many rare diseases are devastating to patients and thus developing effective therapies represents an urgent unmet need. One way to accelerate the development of new therapies for rare diseases is by using quantitative disease-drug-trial models to maximize the use of available data.

Given the significant impact of MID3 in accelerating the delivery of new therapies for rare diseases, the present manuscript will highlight how *in silico* tools, particularly quantitative disease-drug-trial models, can be applied to guide the development of new therapies for rare diseases. This will be demonstrated in the context of drug development for Duchenne muscular dystrophy (DMD), a rare progressive neuromuscular genetic disease. DMD is a particularly motivating example as it is a debilitating, fatal disease with no curative treatment yet identified. Furthermore, in Duchenne, muscle degeneration occurs in patients who are also gaining strength due to growth and development, so changes in endpoints are non-linear. Although companies are investing in new treatments for DMD, development programs are challenging due not only to the limited access to clinical data for this rare disease, but also because the type, number and relevance of endpoints to assess disease progression vary across the disease continuum. Hence, the goal of the present manuscript is to illustrate how some of the clinical development challenges in rare diseases such as DMD can be overcome through collaborative data sharing and modeling and simulation efforts as demonstrated by the Duchenne Regulatory Science Consortium (D-RSC).

Case study: advancing drug development tools for Duchenne muscular dystrophy

Disease overview

Duchenne muscular dystrophy is a fatal genetic X-linked disorder that primarily affects males and impacts patients worldwide. Prevalence of the disease is approximately 1.38 per 10 000 male individuals aged 5 to 24 years [10], which means that it is considered an orphan disease. Duchenne is caused by mutations in the gene that encodes dystrophin, which is the largest gene in the human body [11]. Patients are usually diagnosed in early childhood, when characteristic signs of muscle weakness such as the Gower's maneuver (i.e., using hands to push off the thighs to stand up) may be recognized, followed up with a genetic diagnosis of the disease [11]. As patients grow older, their muscles continue to degenerate, and weakness progresses. While the rate of progression is highly variable between patients, the progression of symptoms occurs in a predictable order. Patients lose the ability to stand up from lying down, climb stairs, walk (typically between age 7 and 15), followed by progressive loss of upper body strength including loss of ability to get their hands to their head to groom, to mouth to eat to the table to perform table top activities [12, 13]. Premature death typically has been reported to occur due to cardiomyopathy or respiratory decline by age 15-30 years [14–16], although patients are now surviving longer due to interventions.

The first approvals for DMD drugs have been obtained, however, none of these treatments provide a cure for the disease. Corticosteroids (prednisone or deflazacort) are considered standard of care for DMD [14] and slow disease progression. Emflaza™ (deflazacort) was approved for DMD by the US Food and Drug Administration (FDA) in 2017, while prednisone is used off-label [14]. The exact mechanisms of steroids in DMD is not fully elucidated, but may relate to anti-inflammatory activity and/or stabilization of muscle membranes, and their use has been shown to delay loss of ambulation and potentially slow respiratory decline [12, 13]. Translaren™ (ataluren), which targets nonsense mutations, received conditional marketing authorization for use by the European Medicines Authority (EMA), but has not been approved in the United States. Exondys 51™ (eteplirsen), an oligonucleotide that targets specific mutations amenable to exon 51 skipping, was given accelerated approval by the FDA in 2016 and has not been approved in Europe. Data suggest that while all four drugs may slow the disease, none is able to stop progression or reverses symptoms. Additional therapies are under development, including additional treatments that aim to patch over specific mutations, gene therapies aimed at

replacing dystrophin with a functional microdystrophin and therapies aimed at downstream processes that might slow progression and/or increase muscle strength [17]. Advocacy groups list over 30 interventions currently under investigation for DMD [18], and 31 interventional clinical trials for Duchenne are listed as recruiting or soon to open for recruitment on clinicaltrials.gov [19].

While drug development for DMD has accelerated over the past decade, the consequent growth in the number of clinical trials represents a drug development challenge, and there remain many areas where drug development tools are needed. In rare diseases where the number of patients with the diseases is limited, sponsors must compete for study participants. This is further exacerbated by the fact that most endpoints used in Duchenne trials can only be effectively measured in patient subgroups at specific disease stages [12, 13], with most trials targeting older ambulatory patients only. In younger patients, the disease progresses in parallel with growth and development up to seven years of age, meaning that patients may exhibit a temporary net gain in strength or abilities, albeit to a lesser extent than in healthy children of the same age. As patients age, these gains plateau and then are lost as the disease progresses, with rates of decline and loss of function varying depending upon the function being assessed [12, 13]. The significant variability in functional ability at baseline and the rate of progression for individual patients makes it difficult to choose a primary endpoint that will reflect changes in the disease for the larger DMD population over the short period of a trial, as well as increasing the complexity of developing clinical outcome assessment instruments. Furthermore, this variance requires large numbers of patients in each trial, and for each trial to be performed over longer periods in order to detect a drug effect. Unless improved clinical trial designs are identified which mitigate these challenges, it will remain extremely difficult to conduct studies in DMD patients with adequate sample size and sufficient power to yield definitive results, and patients will continue to take part in trials over long periods, which may not lead to meaningful improvements in their disease.

Rationale for a consortium-based approach

Although MID3 principles have been widely embraced throughout the pharmaceutical industry, a major determinant in the application and impact of modeling and simulation is access to data. In the context of rare diseases, due to limited population sizes, fewer studies and smaller clinical trials have been conducted, which may also be compounded by individuals participating in multiple studies (which leads to a biased reduction in the estimated variability, and could be easily resolved by the adoption of common unique subject identifiers). Access to quality informative data is often gained through cooperative natural history studies, which in the case of DMD provide the largest datasets across a broad group of patients; however, even these are limited in size, with the largest containing less than 500 patients [20–22]. Interventional studies are much smaller (fewer than 300 patients) and may have relatively tight inclusion criteria based on the study endpoint [23–26]. Such data limitations have significant implications when attempting to generate clinical trial simulation platforms, as quantitative disease-drug-trial models—especially those built using a "top-down" approach—require access to clinical datasets of sufficient size to maximize the likelihood that models will reflect the characteristics and variability in the target patient population. Moreover, a standard practice in drug development is for drug sponsors to conduct independent modeling and create proprietary simulation tools to support their specific drug development programs based on their own internal databases. The result of this practice in the context of rare diseases is that such "proprietary" models are built on relatively small numbers of patients and few studies, thus not reflecting the patient population. This leads to greater model uncertainties and net inefficiencies in the drug development process, given the redundancy in model development and regulatory review, and often precludes the broader scientific community from the lessons learned from these efforts. The net result for rare diseases is that in the absence of data sharing and open access to tools there may be little consensus around how a disease progresses across its continuum, or what a clinically meaningful therapeutic effect might look like.

Consortia that bring together multiple sponsors and academic researchers create an opportunity for sharing of data and collaborative modeling and simulation efforts. This is based on the premise that groups with access to informative datasets may be willing to share available data in a pre-competitive setting, such that the integrated dataset available for analysis may be significantly larger, thereby increasing the representativeness of the patient population and predictive performance of the models. If multiple datasets from different sources can be brought together and integrated in a meaningful manner and applied to develop *in silico* tools, a wider spectrum of the patient population can be characterized, and more causes for variability may be identified. Furthermore, access to multiple datasets often allows models to be built on part of the dataset (training set) and validated in another (validation set), increasing confidence in the models ability to predict disease progression.

The consortium approach is being applied in DMD to promote data sharing in the pre-competitive space to enable the development of *in silico* tools to mitigate drug

development gaps. D-RSC seeks to improve the delivery of new therapies through development and application of quantitative disease-drug-trial models to optimize clinical trial design. The D-RSC consortium was founded in 2015 through a partnership between the Critical Path Institute and Parent Project Muscular Dystrophy, a non-profit patient advocacy organization focused on Duchenne muscular dystrophy. D-RSC currently includes seven company members, 16 academic advisors, representatives from the Duchenne patient and patient advocacy communities, and has liaisons from the FDA, EMA, and the US National Institute of Health (NIH).

The D-RSC Consortium has accessed data from 12 different studies, of which 11 studies contributed to the modeling analysis dataset (Table 1). These include control arms from clinical trials, natural history data sets and collections of clinical data. Data custodians share data with the consortium through data sharing agreements that specify how the data might be used, and who might have access to the data, and the owners of the data frequently join the consortium. The data are stored in a secure database and only made available as permitted by the custodians. While many data owners are cautious about sharing their data due to concerns about others using their data first, mis-interpretation of data and considerations around ability to keep studies funded going forwards, the consortium approach allowed all data owners insight and input into how their data was being used and influence over any uses and publications, increasing comfort in sharing the data.

Representatives from the member organizations include (a) researchers from data contributing organizations to share prior knowledge for each dataset, (b) clinicians to ensure that the data will be interpreted in a clinically relevant manner, (c) patients to ensure that the proposed tools measure aspects of disease relevant to patient experience, and (d) multiple sponsors to promote consensus on the key gaps in drug development that may be resolved through one or more *in silico* drug development tools. This mix of stakeholders has prompted robust discussions during consortium startup to ensure that the final deliverables will meet the needs of drug developers while respecting stakeholders in the broader community. By working together to build a collaborative drug development toolkit with buy-in from multiple parties, the final product is more likely to be agreed upon by all stakeholders, used by sponsors, and acceptable to the community as a whole.

Application of data standards

The development of informative models that describe the entire disease continuum in rare diseases starts with the aggregation of data from multiple studies into a single database, which presents several challenges. In different studies, there may not be standardization with respect to collection of clinical endpoints and recording of variables. For example, in the DMD literature, "loss of ambulation" has been defined in several ways—inability to complete the 6-min walk [27], inability to complete the 10-m walk/run test [12], and inability to walk a single step [28]. Combining such raw values would create a nonsensical variable, an issue which, while not uncommon even in widely studied diseases, is an even greater challenge in rare diseases where the number of datasets for aggregation is limited. Different studies may also collect the same endpoints in slightly different ways, making results incomparable—for example, some studies allow encouragement during performance of the 6-min walk distance, while others do not. Furthermore, different studies typically collect different clinical endpoints, with few studies collecting all endpoints that may be of interest to the modeler. In DMD, most datasets are based on ambulatory status, and are therefore lacking in critical clinical endpoints that encompass the spectrum of the disease. Even within ambulatory datasets, some studies focus on a limited selection of endpoints, although consensus is building around a minimal basic dataset [29]. Each dataset is focused on data collected for a specific purpose and different subpopulations. This makes linking models of progression across disease stages challenging.

Integrating data from multiple studies in a scientifically meaningful way requires standardization of variables to ensure that only equivalents are combined. To promote data standardization, D-RSC has partnered with the Clinical Data Interchange Standards Consortium (CDISC) to develop a Therapeutic-Area User Guide (TAUG) for DMD [30]. Data standards developed by CDISC are an accepted way to standardize clinical data and detail records of differences among studies. The TAUG for DMD promotes the use of data standards by describing how to apply the CDISC data structure to measurements specifically used in DMD studies, including how to document differences in techniques that may be used to collect such data. This guide, which is publicly available, was developed by a multi-disciplinary working group, includes concept maps that reflect how each measure was performed in multiple DMD studies and how the data was recorded. These maps were translated into data elements that can be used to note differences between studies in the aggregated database, ensuring that only equivalent variables were combined. Application of the CDISC data standards has enabled D-RSC to aggregate data from multiple studies into a single database for use in modeling and simulation efforts. A summary of the studies characteristics is presented in Table 1, which are discussed in the context of specific challenges for model development in DMD.

Development of a disease progression model for DMD

One of the main objectives of D-RSC is to utilize the aggregated data to develop a model-based clinical trial simulation tool to optimize the design of clinical efficacy studies in DMD. The intended context of use for this tool is described in Box 1 and will be based on quantitative disease-drug-trial model(s) describing disease progression as measured by a series of stage-specific clinically relevant outcomes (Table 2). The time metric for the models is years of age for individuals in the analysis dataset. Age was chosen instead of time in the study for three main reasons: (a) motor function in Duchenne patients is age-dependent, (b) some studies in the dataset do not carry time in the study, and (c) data included a wide range of ages at study entry.

General modeling and simulation strategy

The development process of the multivariate or univariate DMD progression model(s) is illustrated in Fig. 1. Briefly, separate models will be developed for each of the outcomes of interest, which will consist of mathematical functions that describe changes over years of age for each of the dependent measures, followed by the incorporation of two levels of random effects for between-individual variability (BIV) and residual variability (RV). For the natural disease component, linear models will be tested followed by non-linear models of increasing complexity. Bounded variables such as the North Star Ambulatory Assessment may be treated as continuous outcomes, and thus a beta distributed RV structure may be investigated, in addition to other methods, from the Wilcoxon approach to logistic quantile regression. In the beta distributed RV structure, the scores are subject to ceiling and floor effects, which cause the RV to be heteroscedastic with the variance approaching zero when the mean is close to the boundaries of the scale [31].

Although models will be initially developed independently for each outcome of interest, if the individual models perform well in simulation-based diagnostics, the models will be attempted to be brought together into a multivariate model. A multivariate model including most of the outcomes of interest has advantages for clinical trial simulation of multiple outcomes and is expected to be feasible based on the aggregated analysis dataset. First, there appears to be sufficient overlapping data with respect to collection of various ambulatory assessments within the same individuals and across a reasonable age range. Second, exploration of the analysis dataset indicates that values from such ambulatory assessments are highly correlated. Hence, a multivariate model that allows information to be borrowed among the various ambulatory assessments should be feasible, which may also increase the power to assess the extent in which covariates can explain the variability in multiple clinical measures.

Covariates for potential inclusion in the model(s) have been pre-specified based on prior knowledge and/or clinical interest and are presented in Table 3. As efforts are focused on estimation of covariate effects, covariate modeling will be initiated using a "full model" approach in which all covariates will be included a priori. This may be refined based on the estimated precision and the identified clinical relevance of estimated covariate effects to generate a "parsimonious model", which may also enhance model stability in the case of the computationally intensive methods used in the multi-state Markovian model for categorical outcomes (viz., for the Brooke Scale). In this context, effects of different covariates can be included on different multi-state model transitions in the parsimonious model, whereas the full model will include all covariates on all transitions. At each stage of covariate modeling,

Box 1 Proposed context of use statement for the DMD model

General area: Clinical trial simulation (CTS)

General description: A disease progression model-based CTS tool designed to optimize clinical trial enrichment and design of studies to investigate efficacy of potential therapies for Duchenne Muscular Dystrophy (DMD). Measurements of DMD disease progression will be based on changes in a series of endpoints—velocities of completion of the supine-stand test, 4-stair climb test, 10-meter walk/run test and 30-foot walk/run test, forced vital capacity, North Star Ambulatory Assessment and the transition between scores in the Brooke scale

Target population for use: Individuals with DMD 4 years and older (endpoint-dependent), regardless of stage of disease

Stage of drug development for use: All clinical efficacy evaluation stages of drug development in DMD, including early efficacy, proof-of-concept, dose-ranging, and registration studies

Intended application: To help inform, through simulations, the definition of inclusion/exclusion criteria, enrichment strategies, stratification approaches, timing and selection of clinical assessments, trial duration and sample size for studies evaluating therapeutic candidates for DMD

Out of scope: Clinical trial simulations based on this model should be considered in the context of additional aspects (e.g. characteristics of the individual population, clinical pharmacology and safety of potential therapies) and are not intended to replace the performance of actual clinical trials for the assessment of safety and efficacy

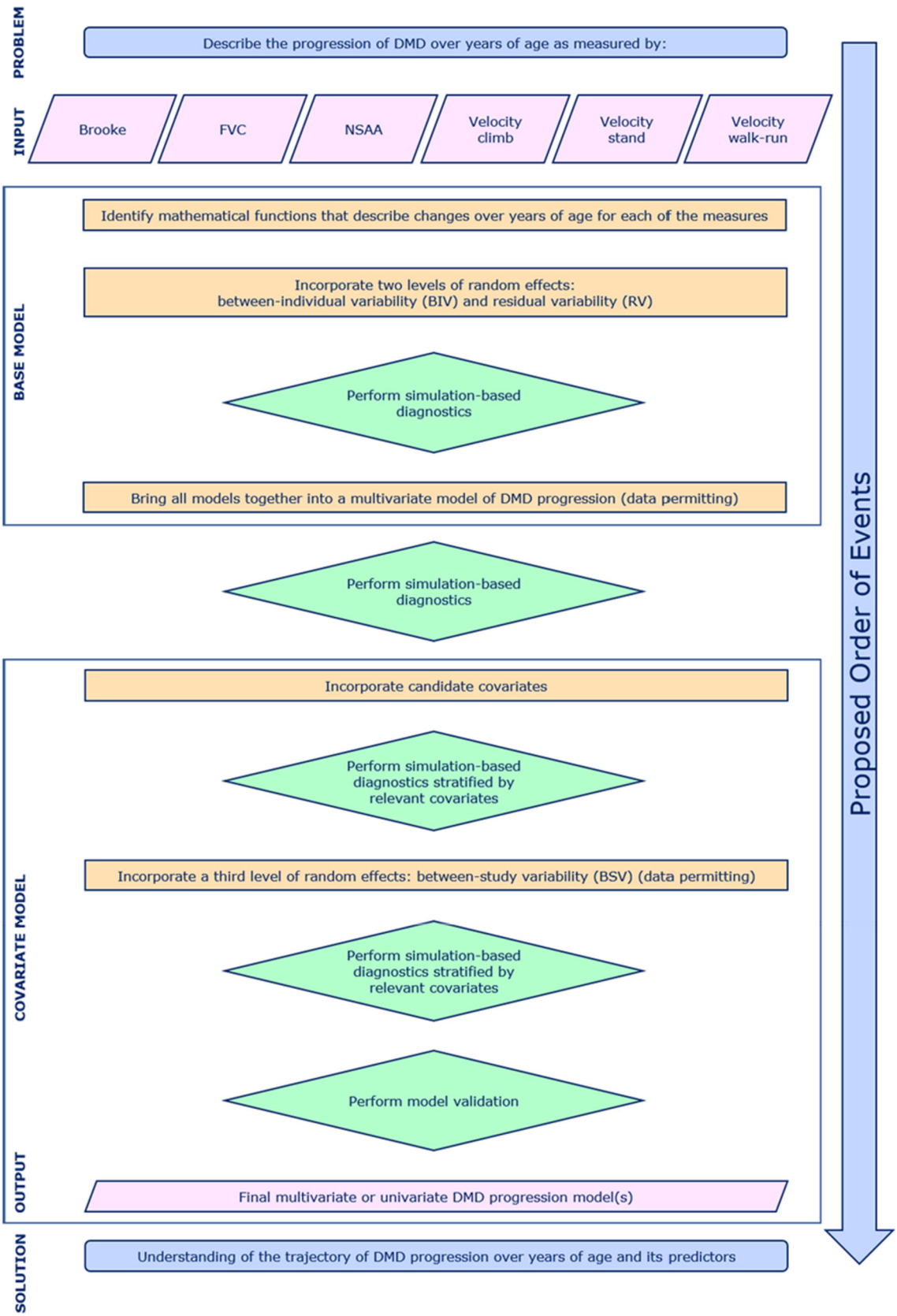

Fig. 1 Proposed development and evaluation process of the DMD multivariate or univariate progression model(s). DMD = Duchenne muscular dystrophy; FVC = Forced vital capacity, NSAA = NorthStar ambulatory assessment

model performance will be evaluated using simulation-based diagnostics, with stratification by relevant covariates. Once reasonable model performance is achieved, incorporation of a third level of random effects (between-study variability, BSV) will be attempted, which allows to account for unobserved variation between studies and is especially important if studies do not seem comparable—i.e. different standards of care due to location/time period the study was performed in; specific inclusion and exclusion criteria as mentioned above; different follow-up schedules and type of study and therefore levels of care potentially (natural history vs. registry vs. trial data). Simulation-based diagnostics will be repeated, followed by model validation to yield the final DMD disease progression model(s). No attempt will be made to model the effect of ataluren or eteplirsen on Duchenne disease progression, due to lack of data available on patients taking these interventions at this time. Use of corticosteroids (deflazacort and prednisone) will be incorporated as covariates, demonstrating their effects on disease progression. Due to lack of detailed dosing data, steroid use can be defined by type of steroid, age at start of steroid use, and whether the patient is currently using steroids, used them in the past or never used them; further details of drug regimen are not available.

Challenges specific to DMD disease progression modeling

Although the general framework outlined above relies on standard modeling and simulation practices, specific challenges related to the DMD modeling effort have been identified which must be addressed. As mentioned previously, one of the challenges in modeling and simulation in the context of rare diseases is the need to aggregate multiple studies to build a dataset that is sufficient to support model development. This is the case for the D-RSC modeling effort, where longitudinal individual-level data from 11 studies in individuals diagnosed with DMD were identified and integrated following CDISC standardization (Table 1). The final analysis data set (i.e., after exclusions), disregarding missing observations, included a total of 1139

Table 1 Characteristics of the studies in the proposed analysis dataset[a]

Study (assigned identification)	Type of data	Number of individuals	Number of observations	Age range in years	Mean duration of follow up in years [range]	Dependent variables
UC Davis (DMD-1000)	Natural history	60	527	4–31	3.3 [0–10.3]	Brooke, FVC, velocity climb, stand, walk-run
UC Davis 2 (DMD-1000A)	Test/re-test data for clinical outcome assessment	24	226	4–14	0.8 [0–1.6]	Brooke, velocity climb, stand, walk-run
CCHMC (DMD-1002)	Clinical	96	1697	4–17	6 [0–9.2]	FVC, NSAA, velocity climb, stand, walk-run
CINRG DNHS (DMD-1003)	Natural history	440	11,475	4–34	4.5 [0–9.9]	Brooke, FVC, NSAA, velocity climb, stand, walk-run
Santhera (DMD-1004)	Placebo arm of trial	34	392	10–19	1 [0.3–1.1]	Brooke, FVC
Lilly (DMD-1005)	Placebo arm of trial	116	2556	7–15	0.9 [0–1.1]	FVC, NSAA, velocity climb, stand, walk-run
CHOP (DMD-1006)	Clinical	42	79	5–24	1 [0–3.3]	FVC
Imaging DMD (DMD-1007)	Natural history	91	738	5–18	1.9 [0–4.1]	Velocity climb, stand, walk-run
PTC 007 (DMD-1009)	Placebo arm of trial	57	1515	5–16	0.9 [0.8–1]	Velocity climb, stand, walk-run
PTC 020 (DMD-1010)	Placebo arm of trial	115	3023	7–15	0.9 [0–1]	NSAA, velocity climb, stand, walk-run
CINRG steroid (DMD-1011)	Clinical trial of steroids	64	1982	4–12	1 [0.2–1.7]	Brooke, FVC, velocity climb, stand, walk-run

UC University of California, *CCHMC* Cincinnati Children's Hospital Medical Center, *CINRG* Cooperative International Neuromuscular Research Group, *CHOP* Children's Hospital of Philadelphia, *FVC* Forced vital capacity, *NSAA* NorthStar Ambulatory Assessment

[a]Numbers calculated after exclusions and disregarding missing observations

individuals with DMD with 24 210 (non-missing) observations of the dependent variables from 4 to 34 years of age. It is possible that some of the patients represented in these studies overlap, it is unlikely that there is much duplication due to studies being performed in different places and periods of time, and the fact that the clinical trials were all more contemporary and patients could not enroll in multiple trials. While this represents, to our knowledge, the largest dataset of clinical data from DMD patients ever compiled for analysis, aggregation of diverse studies has resulted in specific challenges that must be addressed during modeling and simulation efforts. While all but one study dataset contained some overlapping data elements and could be used for modeling, most study datasets contained only a subset of the outcomes of interest and included patients within a narrow range of inclusion criteria. Further, most studies did not collect information on all covariates of interest and, when present, were heterogenous in how covariate data were collected across studies. Beyond highlighting the importance of standardization regarding data collection and recording in the context of clinical trials, the inconsistency in covariate data across studies necessitates that missing covariate data must be carefully considered. For example, imputation of categorical covariates values (e.g., race, steroid use, genetic mutation) will not be performed, but rather an additional category for "missing" will be included, with consideration given when a large proportion of covariate information is missing. In contrast, for certain continuous covariates (e.g., baseline scores, body mass index) model-based imputation methods may be utilized.

A related challenge is missing dependent variable data, when the missingness may or may not be informative, including (a) missing observations due to the inability to perform a test because of disease progression (e.g., walk in a walk-run test) and (b) missing observations due to dropouts, which are likely not-at-random (biased toward more rapidly progressing patients, so those remaining are more highly functioning subgroup). In the former case as this represents data that is not quantifiable when patients drop below a certain threshold of assessment feasibility (analogous to samples below a quantification limit), missing observations will be censored and standard methodologies such as the likelihood-based M3 method [32, 33] will be used during estimation. Regarding the latter, while dropout is not a specific challenge for rare diseases, a major consideration in the case of DMD is that patient mortality is expected to be a major reason for study dropout, especially at older ages (e.g., late teenage years and beyond). Because missingness due to death is expected to be informative, accepted approaches for handling patient dropout (i.e., parametric time to event models) will be accompanied by a simulation-based sensitivity analysis to evaluate the impact of known factors related to DMD mortality [10, 34–37].

Lastly, the interplay between the available clinical trial data for analysis and the scope of the proposed models which are intended to capture disease progression across the entire continuum of DMD patients poses yet another challenge in the selection of appropriate methodologies for assessing model validity (e.g., predictive performance). Model validation, especially for models submitted for formal regulatory review, is often conducted through demonstration of adequate model performance when applied to an independent dataset (i.e., data from external sources not included in the model building dataset). However, as seen in Table 1 this approach may not be feasible as only one dataset, a natural history study from the Cooperative International Neuromuscular Research Group (CINRG), contained all outcomes of interest and included patients across all age ranges. This study also represents the largest source of individual subjects and data points in the analysis dataset, necessitating that data from this study be included in model building (along with other datasets to help broaden the population beyond this study), thereby precluding its use as an external validation set. To address this issue, k-fold cross-validation [38] will be utilized for model validation in place of an external validation approach. Briefly, the dataset will be split into k number of subsets, with splits stratified by study and/or to maintain the proportion of data coming from different studies. The model building process will be repeated in all permutations of the k-1 subsets, and the model will be evaluated on each remaining subset. It is expected that this approach will be sufficient to demonstrate model validity while simultaneously maximizing the use of the pooled data for model development.

Regulatory endorsement as a drug development tool

The goal of many consortia is to develop one or more quantitative drug development tools that are of high scientific quality and are broadly applicable across drug development programs in a specific therapeutic area. However, widespread application of drug development tools by sponsors necessitates both a comprehensive communication strategy as well as a high degree of confidence that outputs derived from such tools will be considered accepted as scientifically valid when presented to regulatory authorities. Both aspects are being considered in the case of the D-RSC effort, as it is envisioned that the quantitative disease-drug-trial models will be a powerful drug development tool to optimize the design of future clinical efficacy studies in DMD. While communication of DMD model utility to the broader research community will

utilize standard strategies (i.e., open-access manuscripts, open-source model code, model implementation via web-based graphical user interfaces), formal review and endorsement by FDA and EMA will be sought via mechanisms which are regulatory authority specific (described below). Endorsement in this context means that regulators agree that the drug development tool is appropriate for a specific context of use, an example of which is provided in Box 1 for the DMD quantitative disease-drug-trial model. Regulatory endorsement enables sponsors to apply drug development tools within the defined context of use without requiring case-by-case review of the model and streamlines the review process when the drug development tools are updated and/or applied beyond the context of use. Together, this gives the community confidence in using drug development tools and increases the probability of success in development of informative clinical trial protocols.

The fit-for-purpose initiative (FDA)

The fit-for-purpose (FFP) Initiative provides a pathway for the formal regulatory review and potential acceptance of quantitative tools for use in drug development programs [39]. The process (illustrated in Fig. 2), initiates with a letter of intent (LOI), an executive summary of the briefing document, which in turn represents a description of the proposed context of use, underlying datasets intended for model development and validation, and the modeling analysis plan. The submission of the LOI triggers the formation of the review team at FDA, co-led by the Office of Clinical Pharmacology, and the respective Review Division, with additional representatives from other arms of FDA. After LOI submission and formation of the review team, a pre-submission teleconference is scheduled to determine if the briefing document is ready for submission. Briefing document submission triggers another detailed FDA review, and a potential a face-to-face meeting. Formal feedback from the FDA review allows the submitter to execute the proposed analyses which are ultimately delivered for final review via a formal submission document. This document presents the final modeling and simulation report (i.e., results, validation and outputs, model code), and includes the patient-level dataset used for model development and validation. A drug development tool is deemed "fit-for-purpose" based on the acceptance of the proposed tool following a thorough evaluation of the information provided. This determination is made publicly available to facilitate greater utilization of these tools in drug development programs.

Qualification of novel methodologies (EMA)

As with the FFP process, the Qualification of Novel Methodologies (QNM) pathway provides a formal mechanism for regulatory endorsement of novel drug development tools, including quantitative tools. The scientific advice is given by the Committee for Medicinal Products for Human Use (CHMP) based on recommendations of the Scientific Advice Working Party (SAWP). Unlike the FFP initiative, the QNM pathway is user-fee based and adheres to structured timelines in the review process.

The QNM process is similar to that described for the FDA's FFP process, with initiation via submission of an

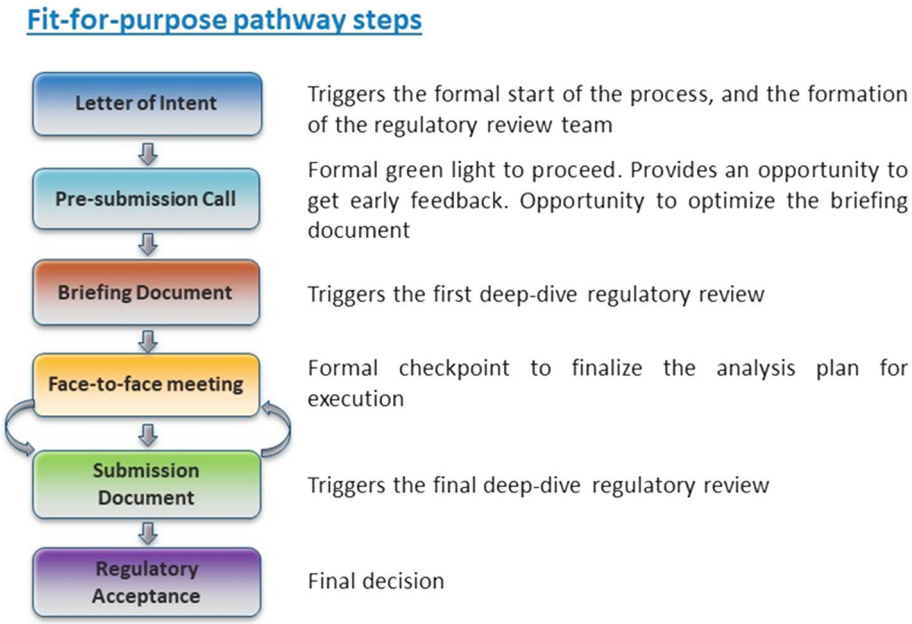

Fig. 2 FDA's fit-for-purpose initiative process for the review and regulatory endorsement of quantitative drug development tools

Table 2 Dependent variables to be modeled

Endpoints	Description/rationale	Range/Grading scale ("normal/mild" in italics, "severe/worst" in bold)
Brooke upper extremity scale	A 6-point scale that allows classification of upper extremity function and helps document progression	Functional Grades: Arms and Shoulders: *1*—Standing with arms at the sides, the patient can abduct the arms in a full circle until they touch above the head 2—The patient can raise the arms above the head only by flexing the elbow or by using accessory muscles (i.e. by shortening the circumference of the movement) 3—The patient cannot raise hands above the head but can raise an 8-oz. glass of water to the mouth (using both hands if necessary) 4—The patient can raise hands to mouth, but cannot raise 8 oz. glass of water to the mouth 5—The patient cannot raise hands to the mouth but can use the hands to hold a pen or to pick up pennies from a Table. **6**—The patient cannot raise hands to the mouth and has no useful function of the hands
Forced vital capacity (FVC)	FVC: the total volume of air that can be forcibly exhaled from the lungs after taking the deepest breath possible (i.e., during the Forced Expiratory Volume test)	The normal FVC range for an adult is between 3.0 and 5.0 L The average FVC for "average-size" preschool boys and girls are is 1.16 and 1.04 L, respectively
North star ambulatory assessment (NSAA)	A 17-item rating scale that is used to measure functional motor abilities in ambulant children with DMD The 17 items are: 1. Stand 2. Walk 3. Stand up from chair 4. Stand on one leg-right 5. Stand on one leg-left 6. Climb box step-right 7. Climb box step-left 8. Descend box step-right 9. Descend box step-left 10. Gets to sitting 11. Rise from floor 12. Lifts head 13. Stands on heels 14. Jump 15. Hop right leg 16. Hop left leg 17. Run (10 meters)	Each item is graded as follow: *2*—"Normal" i.e., no obvious modification of activity 1—Modified method but achieves goal independent of physical assistance from another **0**—Unable to achieve independently This scale is ordinal with 34 (i.e., 17 items × 2) as the maximum score indicating fully-independent function
Velocity of completion of the 4-stair climb test	The 4-stair climb test is a test of ascending stair activity plus a test of lower body strength and balance. Patients are timed climbing 4 standard sized steps	Velocity was calculated as 1 divided by time to climb 4 stairs
Velocity of completion of the supine-stand test	The supine-to-stand test is a combined assessment of flexibility, strength, locomotion and balance, and overall motor competence. The participants are asked to assume a supine position on a padded mat on the floor. They are asked to stand up as quickly as possible following a 'go' command from one of the research staff	Velocity was calculated as 1 divided by time to stand

Table 2 (continued)

Endpoints	Description/rationale	Range/Grading scale ("normal/mild" in italics, "severe/worst" in bold)
Velocity of completion of the 10-meter walk/run test or 30-foot walk/run test	Time to walk or run 10 meters or 30 feet at a fast pace on an even flat surface	Velocity was calculated as distance divided by time taken to walk or run the respective distance

Table 3 Covariates to be investigated during DMD model development

Covariate	Baseline or time-varying?	Continuous or categorical?	Notes
Age	Time-varying	Continuous	Independent variable
Body mass index (BMI)	Time-varying	Continuous	Models of height or weight versus age will be developed (tentatively in a multivariate fashion). Such model will be used to calculate BMI at various ages in which the endpoints have been collected (model-based imputation)
Race	Baseline	Categorical	
Assessment score	Baseline	Continuous	Score for a given clinical assessment, at the first completed attempt for an individual at baseline. Baseline age may differ by assessment
Steroid use	Time-varying	Categorical	Data allow analysis of prednisone versus deflazacort and "Current user", "Past user", "Steroid Naïve"
Genetic mutation	Baseline	Categorical	Data allow analysis of nonsense mutation versus deletions (separated by exon-skipping group) versus small mutations versus duplications

LOI and briefing package, the contents of which are analogous to those described for the FFP submission with only minor differences. This submission triggers a formal review by EMA's SAWP, which culminates in a face-to-face meeting to discuss the context of use statement and analysis plan and obtain formal scientific advice. Following this meeting, the modeling analyses are executed, and a final qualification package is submitted to EMA upon completion. Following formal review, another SAWP meeting is held to reach a final determination whether the analyses provide sufficient evidence that the drug development tool supports the proposed COU. Outcomes following this meeting are based on recommendations from the SAWP to the CHMP, and may include (a) qualification advice, guidance on additional work to be performed to support qualification, or (b) a qualification opinion, an assessment of whether the drug development tool is acceptable for use within the specified context of use. In the former case, a letter of support from the EMA may be offered along with the qualification advice to encourage researchers to generate and/or share data to support future qualification efforts.

Conclusions

Drug development for rare diseases is frequently challenged by limited understanding of disease natural history and progression, the dynamics of endpoints in the populations studied, and of trial characteristics such as the placebo effect and patient attrition. Model-informed drug development can help drug developers answer these questions and to develop more efficient clinical trial protocols that help give definitive answers as to the potential efficacy of a new therapy, as it focuses on giving the right dose of the right drug for the right target, to the right patient in the right type of clinical trial design. However, several factors need to be in place in order for these models to be developed; large datasets, which may not be readily accessible in rare diseases, the resources/funding to start a consortium to support model development and the willingness of stakeholders to collaborate. Here, as demonstrated by the work of D-RSC, we offer a framework for development of such modeling solutions. In order to develop a rare disease database large enough for modeling, data are integrated from multiple data sources (clinical trials, natural history studies and data from clinical centers) using CDISC standards. Owners of the data and disease experts are part of a consortium that together review and integrate the data, and develop the modeling solutions, ensuring that knowledge from all sectors is included. Once the database is developed, it may be used to develop modeling solutions: in the case of D-RSC a clinical trial simulation tool. This tool will be reviewed by FDA and EMA, through the FDA fit-for-purpose and EMA qualification of novel methodologies pathways. The intended outcome of this review process is the potential regulatory endorsement of the model for a stated context of use, and the tool will be made available to the entire drug development community, and will be able to be used for that

purpose without further justification. This will aid all drug developers in this rare disease by helping them to develop clinical trial protocols that will be informative, while minimizing the numbers of patients and the duration of the trial. It will aid patients through accelerating drug development and reducing the potential exposure to ineffective compounds and helping to gather data that gives definitive answers on efficacious compounds. It will help regulators to efficiently determine a therapy's efficacy for given patient populations. In order to achieve a comprehensive model-informed drug development approach for rare diseases, consortium approaches that involve multiple stakeholders across the drug development and disease communities will be needed as an effective way to deliver such tools.

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Compliance with ethical standards

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