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ARTICLE

Data driven evaluation of healthy volunteer characteristics at screening for phase I clinical trials to inform on study design and optimize screening processes

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Abstract

Protocols for clinical trials describe inclusion and exclusion criteria based on general and compound-specific considerations to ensure subject safety and data quality. In phase I clinical trials, healthy volunteers (HVs) are screened against these criteria that often specify predefined eligibility ranges for vital signs, electrocardiogram, and laboratory tests. HVs are excluded if baseline parameters deviate from these ranges even though this may not indicate underlying pathology, which could delay trial execution. Data from 3365 HVs participating in 9670 screening visits for 94 phase I HV trials, conducted between December 2008 and May 2019 at the Janssen Clinical Pharmacology Unit, were retrospectively analyzed. Commonly predefined protocol ranges were overlaid with HV data to estimate predicted screen failure rates (SFRs). Of the overall population, 91% was White and 64% were men with mean age of 42.8 ± 12.5 years. High predicted SFRs are related to cardiovascular/metabolic (body mass index, heart rate [HR], blood pressure [BP], and corrected QT Fridericia's formula [QTcF]), renal (estimated glomerular filtration rate [eGFR]), liver (alanine aminotransferase [ALT], and total bilirubin), and coagulation (prothrombin time [PT]) parameters. Predicted SFRs increased with age for high systolic and diastolic BP, QTcF interval, and eGFR. In contrast, lower SFRs in the older age groups were seen for low diastolic BP, liver function test, ALT, PT, and total bilirubin. This analysis can be used to inform on study design, protocol inclusion and exclusion criteria, and to optimize the screening process. Data-driven critical appraisal of proposed inclusion and exclusion criteria using a risk-based approach may significantly reduce screen failure rates without compromising subjects' safety.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

In contrast to those enrolled in phase I trials, healthy volunteer (HV) characteristics at screening are not well-described.

WHAT QUESTION DID THIS STUDY ADDRESS?

What baseline characteristics of HVs at screening result in high screen failure rates based on different predefined protocol ranges?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

This analysis can be used to inform on study design and protocol inclusion and exclusion criteria and optimizing the screening process.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

Data-driven critical appraisal of proposed inclusion and exclusion criteria using a risk-based approach may significantly reduce screen failure rates without compromising subjects' safety.

INTRODUCTION

According to the Good Clinical Practice guidelines, the investigator is responsible for ensuring that only eligible subjects are enrolled in a trial.[1] Eligibility is determined based on the protocol's inclusion and exclusion criteria. These are selected to define the target population, taking general and compound-specific considerations into account. For patient trials, the target population is defined by disease/patient classification systems and by outlining allowed or disallowed prior and/or current treatments. In contrast, there is no objective set of characteristics that univocally describes a "healthy volunteer" (HV). As an alternative, eligibility criteria commonly define an HV as the absence of clinically significant findings in medical history, physical examination, and safety parameters, such as vital signs (VS), electrocardiogram (ECG), and laboratory tests, in addition to trial-specific examinations/tests.[2] Minor deviations from reference normal ranges are common in HVs but may not be indicative of underlying disease and/or increased safety risks.[3–7] In fact, when 30 independent variables are assessed at screening, there is an 80% probability that at least one variable is out of range.[8] In a practical approach, most sponsors enforce specific ranges for selected parameters in the inclusion and exclusion criteria based on the safety profile of the Investigational Medicinal Product (IMP) but allow investigators to enroll subjects with minor abnormalities for other safety parameters based on their clinical judgment. Clearly, these predefined ranges can have a substantial impact on HV enrollment and subject safety. Although very strict ranges will result in excessive exclusion of otherwise eligible subjects and unduly delay trial execution, too flexible ranges pose potential safety risks. To address the lack of authority guidance on what abnormalities are acceptable, the German Association for Applied Human Pharmacology (AGAH, 2017) published a consensus document on pivotal eligibility criteria for HV clinical trials with new or more established IMPs.[9] These criteria are an important first step to standardize HV enrollment. Nevertheless, some key criteria are missing, such as the appropriate age range for HV clinical trials or the acceptable body mass index (BMI), whereas other criteria remain ambiguous as they refer to "in relation to clinical context" (e.g., PR interval and pancreas laboratory tests) or to "ranges as defined in the protocol" (e.g., QT interval corrected with Fridericia's formula [QTcF] and blood pressure [BP]).

In this analysis, we provide baseline characteristics of HVs participating in early development clinical trials at a single center and explored the impact on predicted screen failure rates (SFRs) for different predefined ranges. The results of this analysis can be used to inform on study design and protocol inclusion and exclusion criteria, and to optimize screening process.

METHODS

Trials

This is a retrospective analysis of records of HVs screened for enrollment in phase 0 and I clinical trials between December 22, 2008, and May 14, 2019, at a single center, the Janssen Clinical Pharmacology Unit (CPU; Belgium). The CPU executes early development clinical trials exclusively for Johnson & Johnson (J&J) Therapeutic Areas, including Cardiovascular and Metabolism, Infectious Diseases and Vaccines, Immunology, Oncology, Neurosciences, and Pulmonary Hypertension. Only trials with an approved protocol, a protocol number, a study population that included HVs, and a database lock were included in the analysis. All trials were conducted after approval of an independent ethics committee and in accordance with the Helsinki Declaration.

Subjects

HVs were recruited via post, local, and social media, and the CPU website. The prescreening process consisted of a

telephone interview or on-site consultation. If satisfactory, subjects could register for a trial-specific screening visit. Only data collected during trial-specific screening visits were included in the analysis.

Screening data

Assessments during screening typically included medical history (including medication use), collection of demographic data, physical examination, body size, VS (including temperature, respiratory rate, and supine BP after >5 minutes of rest), ECG (supine, after >5 minutes of rest), and safety laboratory tests (including blood, urine, and urine drug screen), in addition to any trial-specific tests/examinations. Repeat tests or rescreening results were excluded from the analysis.

Data capture and analysis

Data collected during screening were captured in ClinBase, an electronic data capture solution. Data were made accessible through an Enterprise Data Lake and analyzed with TIBCO Spotfire.

Results for body size, VS, ECG, and laboratory tests for all HVs screened between December 22, 2008, and May 14, 2019, were pooled. From this database, it was calculated what the predicted SFR would be if different predefined allowed protocol ranges (strict vs. more liberal) were applied. Protocol ranges assessed were those commonly defined in J&J HV clinical trials in addition to the pivotal eligibility criteria for HV clinical trials with new or more established IMPs, as published by the AGAH.[9]

The predicted SFR for each parameter was calculated for all HVs and for different age ranges (18–55, 56–60, and 61–65) reflecting common age ranges in J&J HV clinical trials. Predicted SFRs were calculated as follows:

Predicted SFR = (# unique HV with ≥1 value out of range for that safety parameter) / (# unique HV screened for this parameter).

For all safety parameters, greater than 50 measurements needed to be available to reliably calculate the predicted SFR (limit set arbitrarily).

Statistical analysis

Analysis was conducted in R and the polar chart was produced using the package ggplot2.

For each cutoff, the relationship between the categorical variables "screen failure" (yes/no) and "age category" was investigated using a χ^2 test for independence.

RESULTS

During the study period, 9670 trial-specific screening visits were performed for 94 phase 0 and phase I HV clinical trials at the Janssen CPU (Table 1). Of these 94 trials, 32 were commissioned by the therapeutic area Neuroscience, 30 by Infectious Diseases and Vaccines, 12 by Immunology, 11 by Cardiovascular and Metabolism, seven by Oncology, one by Pulmonary Hypertension, and one by Janssen Diagnostics.

The prescreening process consisted of a telephone interview for 54% and an on-site consultation for 46% of the HVs, respectively.

Subject characteristics

There were 3365 unique HVs that participated in 9670 screening visits during the study period, indicating that HV, on average participated in screenings for approximately three different trials between December 22, 2008, and 14 May 14, 2019. The number of unique trial screening participations ranged from 1 to 24; 3% participated in screening visits for greater than 10 trials, 43% for 2–10 trials, and 54% for a single trial.

The male to female ratio in the population was 64% to 36%. The distribution across ages for all screening visits is shown in Figure 1. Baseline characteristics, demographics, and key safety parameters are presented in Table 2.

Predicted SFR per protocol ranges commonly defined in J&J phase I HV trials and per pivotal eligibility criteria for HVs as published by the AGAH

Predicted SFRs by protocol ranges commonly applied in J&J HV trials are listed in Table 3 for all HVs and per age group.

TABLE 1 Overview of trials in the database

Type	N
Drug-drug interaction	28
FIH (SAD and/or MAD)	26
Bioavailability/bioequivalence	19
Exploratory/proof-of-concept	6
Thorough QT	4
Food effect	3
Mass balance	3
Dose exploration	3
Vaccine shedding	1
Digital health	1

Abbreviations: FIH, first-in-human; MAD, multiple ascending dose; SAD, single ascending dose.

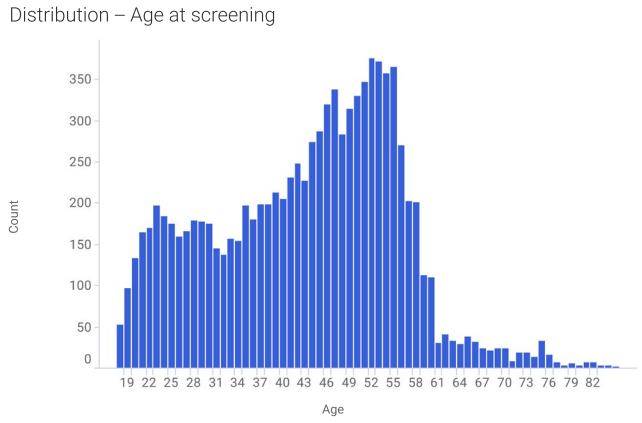

FIGURE 1 Distribution of healthy volunteer age and sex at 9670 screening visits for 3365 unique healthy volunteers. Subjects that participated in screening visits for multiple trials are represented multiple times in the bars

Predicted SFRs for the AGAH criteria are shown in Table 4. The latter are also marked in Table 3 for easy comparison. For some parameters listed in the AGAH consensus document, predicted SFRs could not be calculated as they require additional clinical or protocol details.

Items with the highest predicted SFR are related to cardiovascular/metabolic (BMI, heart rate [HR], BP and QTcF, renal [estimated glomerular filtration rate {eGFR}] and liver [alanine aminotransferase {ALT} and total bilirubin) safety parameters in addition to coagulation (prothrombin time [PT; Figure 2).

Safety parameters for which SFR increased for at least one cutoff and age group (see "Statistical analysis") were high systolic and diastolic BP, QTcF interval, and eGFR (Table 3). In contrast, lower SFR in at least one older age group and cutoff were seen for low diastolic BP, liver function test ALT, PT, and total bilirubin.

DISCUSSION

We described the baseline characteristics of HVs actively screening for early development clinical trials at a single center and assessed the effect of different cutoffs for safety parameter allowed ranges on predicted SFRs. Note, this predicted SFR does not reflect the actual SFR for the individual trials.

Subject characteristics

Overall, demographics and baseline characteristics of HVs in our dataset are in line with those published for other phase I units.[3,5,6,10–15] The mean age of 43 years in our population is generally higher, which could be attributed to the relatively broad age range applied in some of our protocols (generally 18–55 years, and sometimes up to 60 years) and the fact that some studies in our dataset included elderly HV cohorts. With a mean BMI of 25.36 kg/m^2, our population of HVs reflect the global trend of increasing overweight and obesity. Similarly, in the United States, between 1976 and 2012, the average BMI of HV research participants has increased to over 28 kg/m^2.[16] Overweight and obesity in clinical trial participants is of importance as the pharmacokinetic parameters of a drug may be significantly altered in these subjects.[17]

Predicted screen failure rates

Predicted SFRs were calculated for key safety parameters based on commonly predefined ranges in J&J HV clinical trial protocols and those proposed by the AGAH.[9]

Items associated with a high SFR include cardiovascular (BP), renal (eGFR), and liver (ALT and total bilirubin) safety parameters, which is consistent with the observation that approximately half of the subjects participating in screening visits is overweight (BMI >25) or obese (BMI >30).

BPs consistent with arterial hypertension were measured at screening in up to 20% of HVs, less than generally reported for the Belgian population of similar age.[18] Nearly half of HVs aged 61–65 presented with systolic BP greater than 140 mmHg and one third had systolic pressures greater than 150 mmHg. Of note, especially for those volunteers not experienced with clinical trials, a white-coat effect should be considered.

High SFRs were seen for liver function tests. At screening, levels above the upper limit of normal (ULN) were measured in 17% for ALT, 5% for aspartate transaminase, and 11% for total bilirubin. Elevated liver function tests were more common in younger compared to older screening participants. BMI, age, gender, and hormonal oral contraception are all known to be important factors influencing ALT levels, which show considerable day-to-day variation.[19,20] Previously, Wensing et al. reported ALT greater than the ULN for 9.7% of 3217 HVs presenting at screening for phase I clinical trials.[21] Of those with ALT within reference ranges, 6.7% had at least one ALT measurement greater than the ULN while receiving placebo with the highest value exceeding the ULN by a factor of 3.8, hampering early detection of hepatotoxicity.[21,22] Similarly, increases in bilirubin levels may be an early sign of liver toxicity. However, 11% of our HV screening participants had total bilirubin greater than the ULN, in line with other reports.[21,22] The most common cause of elevated bilirubin levels in otherwise healthy subjects is Gilbert's syndrome, present in ~ 5–10% of the population.[23] The diagnosis can be assumed if mildly elevated unconjugated bilirubin is found on at least two occasions

TABLE 2 Healthy volunteer demographics and characteristics across 9670 screening visits

Type	Parameter	All	Unit	Normal range
Demographics	Male/female	64%/36%	%	
	Age	42.9 ± 12.4	y	
	Race			
	Caucasian/White	91%	%	
	Asian/Oriental	2%	%	
	Black/African	2%	%	
	Other	5%	%	
Body size	BMI	25.36 ± 3.02	kg/m^2	18.5–24.9
Vital signs	Systolic blood pressure	122 ± 14	mmHg	<120
	Diastolic blood pressure	74 ± 10	mmHg	<80
Electrocardiogram	Heart rate	64 ± 11	bpm	60–100
	PR interval	108 ± 12	ms	120–200
	QRS duration	96 ± 9	ms	80–100
	QTcF interval	414 ± 19	ms	< 400–440
Blood safety laboratory tests	Hemoglobin–men	14.9 ± 1.0	g/L	12.9–16.4
	Hemoglobin–women	13.2 ± 1.0	g/L	11.0–14.4
	Leucocytes	5.8 ± 1.6	10E9/L	3.45–9.76
	Neutrophils	3.4 ± 1.3	10E9/L	1.6–7.1
	Platelets	242 ± 56	10E9/L	142–340
	Creatinine–men	0.91 ± 0.12	mg/dL	0.66–1.25
	Creatinine–women	0.71 ± 0.10	mg/dL	0.52–1.04
	eGFR	103 ± 14	mL/min	90–120
	ALT–men	36 ± 15	mg/dL	<41
	ALT–women	28 ± 13	mg/dL	<33
	AST–men	29 ± 10	mg/dL	17–59
	AST–women	24 ± 8	mg/dL	14–36
	Total bilirubin	0.72 ± 0.40	mg/dL	0.2–1.3
	Total cholesterol	188 ± 37	mg/dL	≤ 200

Note: Data presented as percentage or mean ± SD. Subjects that participated in multiple screening visits will have multiple data points counting toward the mean.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; eGFR, estimated glomerular filtration rate; QTcF, QT interval corrected with Fridericia's formula.

over 6 months in the absence of elevated serum transaminases, signs of biliary damage/obstructions, or abnormal blood count or blood smear.[23] Nevertheless, whereas benign, enrolling subjects with Gilbert's syndrome as HVs may impede interpretation of bilirubin levels during trials with new IMPs.[9]

Recommendations to optimize inclusion and exclusion criteria

Safety is key in all phases of drug development but especially in HV trials where subjects do not benefit from trial participation. Clearly, logistical or operational considerations, such as SFRs, should not affect the boundaries for inclusion and exclusion criteria, although setting these boundaries too tight will impact subject recruitment. Our analysis provides the basis for a rational and data-driven selection of safety parameters to determine HV eligibility.

Diastolic BP was less than 60 mmHg in 17%, the majority of which were aged 18–55 years with a higher proportion of women (data not shown), consistent with previous observations in both the general population and in phase I trial participants.[15,24] Isolated diastolic hypotension (in the presence of systolic pressures 100–140 mmHg) has been shown to be an independent risk factor for incident heart failure in subjects aged 65+ years, but not in younger subjects.[25] In addition, for the detection of orthostatic hypotension,

TABLE 3 Predicted SFR for commonly applied ranges in Johnson & Johnson HV clinical trials for all healthy screening participants (all) and per selected age range (18–55, 56–60, and 61–65 years of age)

			SFR (%)	SFR (%) per age category				Proportion differences with 95% Wald CI[d]	
Category	**Parameter**	**Cutoff**	**All**	**18–55**	**56–60**	**61–65**	**χ^2[d] test p value[c]**	**SFR 18–55 - SFR 56–60**	**SFR 18–55 - SFR 56–60**
Vital signs	SBP	<90 mmHg	0%	1%	1%	0%	0.562	N/A	N/A
	SBP	>140 mmHg	19%	14%	31%	47%	$p < 0.001$	−17 (−22, −12)	−33 (−43, −23)
		>145 mmHg	14%	10%	22%	39%	$p < 0.001$	−12 (−17, −8)	−29 (−39, −19)
		>150 mmHg	9%	6%	15%	31%	$p < 0.001$	−8 (−12, −5)	−24 (−33, −15)
	DBP	<60 mmHg	17%	18%	9%	1%	$p < 0.001$	9 (6, 13)	17 (15, 19)
		<55 mmHg	4%	5%	1%	1%	0.005	3 (2, 5)	4 (1, 6)
	DBP	>90 mmHg	13%	12%	18%	19%	$p < 0.001$	−6 (−10, −2)	−7 (−15, 1)
		>100 mmHg	3%	3%	5%	5%	$p < 0.001$	−2 (−4, 1)	−2 (−7, 2)
Body size	BMI	>28.0 kg/m[d]	24%	22%	27%	32%	0.015	−5 (−10, 0)	−9 (−19,0)
		>30.0 kg/m[d]	9%	8%	7%	12%	0.339	N/A	N/A
ECG	HR	<40 bpm	1%	1%	1%	1%	0.913	N/A	N/A
		<45 bpm[a,b]	5%	5%	4%	6%	0.418	N/A	N/A
		<50 bpm[a,b]	19%	19%	16%	20%	0.429	N/A	N/A
	HR	>90 bpm[a]	1%	1%	1%	1%	0.584	N/A	N/A
		>100 bpm	0%	0%	0%	0%	0.748	N/A	N/A
	PR interval	>200 ms	7%	6%	8%	13%	0.024	−2 (−5, 1)	−6 (−13, 1)
		>210 ms	4%	3%	5%	6%	0.126	N/A	N/A
	QRS interval	>110 ms	10%	10%	10%	8%	0.779	N/A	N/A
		>120 ms	2%	2%	1%	3%	0.328	N/A	N/A
	QTcF interval – men	>430 ms – M	21%	18%	29%	23%	$P < 0.001$	−11 (−18, −4)	−5 (−17, 6)
		>450 ms – M	3%	2%	5%	4%	0.127	N/A	N/A
	QTcF interval – women	>450 ms – F	10%	9%	14%	ND	0.082	N/A	N/A
		>470 ms – F	1%	1%	0%	ND	0.490	N/A	N/A
Hematology	Hemoglobin	<LLN	3%	3%	4%	4%	0.686	N/A	N/A
		<10.5 g/dL	1%	1%	0%	4%	$p < 0.001$	1 (0, 1)	−3 (−7, 1)
	Leucocytes	<LLN	4%	4%	3%	5%	0.727	N/A	N/A
		<2.000	0%	0%	0%	0%	0.932	N/A	N/A
	Neutrophils	<LLN	4%	4%	3%	5%	0.477	N/A	N/A
		<1.500	2%	2%	2%	2%	0.765	N/A	N/A
	Platelets	<LLN	3%	3%	2%	7%	0.128	N/A	N/A
		<100.000	1%	0%	1%	3%	0.003	−1 (−2, 1)	−3 (−8, 2)
Biochemistry	Creatinine	>ULN[a]	4%	3%	2%	4%	0.684	N/A	N/A
		>1.1*ULN[b]	1%	1%	1%	0%	0.733	N/A	N/A
	eGFR	<80 ml/min	6%	5%	14%	ND	$p < 0.001$	−9 (−16, −3)	ND
		<90 ml/min[a]	18%	16%	31%	ND	$p < 0.001$	−15 (−24, −6)	ND
	ALT	>ULN[a]	17%	17%	16%	11%	0.327	N/A	N/A
		>1.1*ULN[b]	14%	14%	12%	8%	0.225	N/A	N/A

(Continues)

TABLE 3 (Continued)

Category	Parameter	Cutoff	SFR (%)	SFR (%) per age category			χ^d test p value[c]	Proportion differences with 95% Wald CI[d]	
			All	18–55	56–60	61–65		SFR 18–55 - SFR 56–60	SFR 18–55 - SFR 56–60
		>1.25*ULN	7%	7%	4%	4%	0.038	3 (1, 6)	4 (0, 8)
	AST	>ULN	5%	5%	4%	4%	0.825	N/A	N/A
		>1.2*ULN[b]	2%	3%	1%	1%	0.062	N/A	N/A
		>1.25*ULN	2%	2%	1%	1%	0.091	N/A	N/A
	Total bilirubin	>ULN	11%	11%	7%	6%	0.024	4 (1, 7)	5 (0,11)
		>1.1*ULN	7%	7%	4%	5%	0.068	N/A	N/A
		>1.25*ULN	5%	5%	2%	2%	0.035	3 (1, 5)	3 (−1, 6)
	Amylase	>ULN[a]	2%	2%	3%	ND	1.000	N/A	N/A
	Lipase	>ULN[b]	3%	3%	4%	ND	0.683	N/A	N/A
Coagulation	PT (s)	>ULN	43%	44%	31%	24%	$P < 0.001$	13 (7,19)	20 (10, 31)
		>1.1*ULN	6%	6%	0%	12%	$P < 0.001$	6 (5, 7)	−6 (−14, 2)
		>1.25*ULN	0%	0%	0%	0%	0.840	N/A	N/A
	INR	>ULN	1%	1%	0%	0%	0.233	N/A	N/A
	APTT	>ULN	12%	12%	12%	7%	0.436	N/A	N/A
		>1.25*ULN	2%	2%	2%	0%	0.519	N/A	N/A
Homology	TSH	<LLN[a,b]	2%	2%	ND	ND	ND	ND	ND
		>ULN[a,b]	2%	2%	ND	ND	ND	ND	ND

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; APTT, activated partial thromboplastin time; BMI, body mass index; CI, confidence intervasl; DBP, diastolic blood pressure; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; F, female; HR, heart rate; HV, healthy volunteer; INR, international normalized ratio; LLN, lower limit of normal; M, male; N/A, not applicable; ND, not determined as <50 datapoints available; PT, prothrombin time; QTcF, QT interval by Fridericia's correction; SBP, systolic blood pressure; SFR, screen failure rate; TSH, thyroid stimulating hormone; ULN, upper limit of normal.

[a]German Association for Applied Human Pharmacology (AGAH) pivotal eligibility criterion for trials with new IMP.

[b]AGAH pivotal eligibility criterion for trial with established IMP.

[c]Chi-Square test for testing the null hypothesis that there is no relationship between the categorical variables Screening Failure and Age Category versus the alternative that there is a relationship.

[d]Proportion differences with 95% Wald CI are calculated when the $\chi 2$ test indicates a relationship between Screening Failure and Age. A negative upper and lower limit of the Wald CI suggests a higher SFR for the higher age category.

diastolic BP seems to be of limited value.[26] Therefore, it seems reasonable to abandon a specific lower limit for diastolic BP of 60 mmHg for enrollment of young HVs, which could markedly reduce SFRs without compromising subjects' safety.[15]

Almost one in five HVs had an HR below 50 bpm and one in 20 below 45 bpm, the lower ranges for HV enrollment proposed by the AGAH.[9] This is higher than the 8.1% less than 50 bpm reported by Hingorani, based on the baseline records of HVs participating in phase I clinical trials.[4] Subjects with an HR less than 50 bpm were of similar age compared to those with an HR greater than 50 bpm (40.46 ± 10.54 vs. 40.31 ±10.74, ns) but more often were men (82.5% vs. 64.8%). Sinus bradycardia in otherwise healthy subjects with an active lifestyle is linked to increased vagal tone and in clinical practice deemed acceptable up to even 30 bpm if without symptoms.[27] Therefore, it seems reasonable to allow subjects with HRs below 50 or even 45 bpm to enroll in an HV clinical trial, if at least the risk of bradyarrhythmia is considered limited based on the IMP profile and there is no underlying medical condition that is the likely cause of low HR.

PT as a measure of tissue-factor pathway of blood coagulation, was above the ULN for 44% of HVs. The PT, expressed in seconds, is strongly dependent on the nature of the thromboplastin and the laboratory methods used and may yield different results depending on the quality of the thromboplastin.[28] The International Normalized Ratio (INR) is a derivative of the PT, calculated as a ratio of the subjects' PT to a control PT standardized for the potency of the thromboplastin reagent in a calibration model and therefore more consistent.[28] In our database, INR was within normal ranges for nearly all subjects, indicating normal functioning of the extrinsic and common coagulation pathways, despite prolonged PT. These results favor INR as the most appropriate safety parameter for coagulation in HV trials.

TABLE 4 Predicted screen failure rate for pivotal eligibility criteria for HV enrollment as proposed by the German Association for Applied Human Pharmacology for all screening participants (all) and per selected age range (18–55, 56–60, and 61–65 years of age)

			SFR (%)	SFR (%) per age category		
Parameter	**IMP**	**Cutoff**	**All**	**18–55**	**56–60**	**61–65**
HR	New/established	<45 bpm[a,b]	5%	5%	4%	6%
		<50 bpm[b]	19%	19%	16%	20%
		>90 bpm	1%	1%	1%	1%
Creatinine	New	>ULN	4%	3%	2%	4%
	Established	>1.1*ULN	1%	1%	1%	0%
eGFR	New/established	<90 ml/min	18%	16%	31%	ND
ALT	New	>ULN	17%	17%	16%	11%
	Established	>1.1*ULN	14%	14%	12%	8%
AST	New	>ULN	5%	5%	4%	4%
	Established	>1.2*ULN	2%	3%	1%	1%
Total bilirubin	New	>ULN[c]	11%	11%	7%	6%
	Established	>1.2*ULN[c]	7%	7%	4%	5%

Parameter	**Guidance**
ECG – QTcF	Within normal ranges as defined in the protocol
ECG - PR interval	First degree atrioventricular block seems acceptable if heart rate complies with the inclusion criteria and the AV block is not interpreted as a sign of cardiac dysfunction/disease
Blood pressure	Acceptable ranges should be defined in the protocol
Labs - amylase and lipase	Should be interpreted in clinical context
Labs – TSH	Recommended to include to rule out hypo- or hyperthyroidisms

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; HV, healthy volunteer; IMP, Investigational Medicinal Product; ND, not determined if <50 datapoints available; QTcF, QT interval by Fridericia's correction; SFR, screen failure rate; TSH, thyroid stimulating hormone; ULN, upper limit of normal.

[a]For new IMP, consider if heart rate <50 and ≥45 bpm acceptable in case of normal thyroid function (medical history, physical examination, and normal TSH) and no signs of diseases associated with bradycardia plus, if required, normal cardiological examination (including echocardiography and ergometric stress test); take risk-adapted approach.

[b]For more established IMP, consider if heart rate <50 and ≥45 bpm is acceptable in case of normal thyroid function (medical history, physical examination, and TSH) and no signs of diseases associated with bradycardia (e.g., orthostasis and dizziness). Consider if heart rate <45 bpm is acceptable in case of above stated criteria plus normal cardiological examination (including echocardiography and ergometric stress test); take risk-adapted approach.

[c]Except in Gilbert's disease; although not clinically relevant, elevated bilirubin may hamper interpretation of potential drug effects in case of Gilbert's disease.

The difference in SFRs for creatinine and eGFR is consistent with the notion that the latter is a more sensitive test for reduced kidney failure.[29] Whereas creatinine levels are determined by muscle mass, dietary intake, gender, and ethnicity with high interperson variability, eGFR takes age and gender into account and can be indexed for body surface area to account for increased body size.[6,30] Even though a limitation of the eGFR is the greater inaccuracy in populations without known chronic kidney disease,[29] it seems prudent to advise the use of eGFR over creatinine as the safety parameter of choice because even in a young, healthy population, 16% of subjects have an eGFR less than 90 ml/min, which could put them at risk for IMPs with potential nephrotoxicity or distort results of pharmacokinetic parameters for IMPs that are highly dependent on the kidneys for clearance.

Currently, the older population (above age 60 years) are limited in HV studies, however, people are living longer in better health conditions and it could be considered to widen the age range allowed in phase I studies. This would not be acceptable for first-in-human studies, thorough QT studies, or for IMP with findings in cardiovascular safety pharmacology or known cardiovascular class effects, but may be considered for studies with more established IMPs (e.g., bioequivalence studies). If the age range is extended to 65 years, we recommend more flexible inclusion and exclusion criteria, such as systolic BP less than 150 mmHg and BMI greater than 30.0 kg/m^2. Otherwise, the high predicted SFR for these safety parameters will not warrant targeting this age range for screening.

Strengths, limitations, and future perspectives

This analysis presents predicted SFRs for commonly defined protocol ranges that can be used to inform on study design

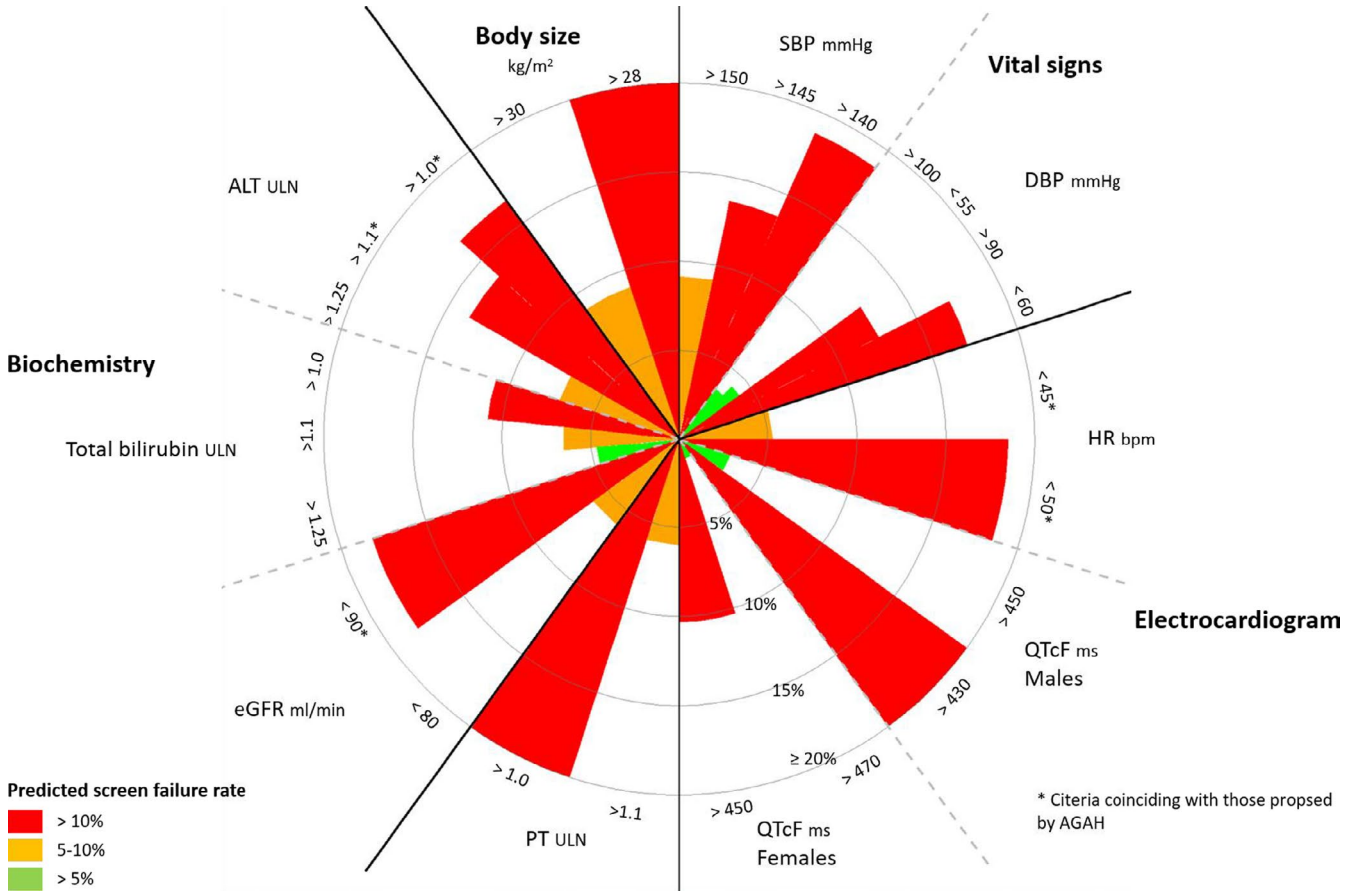

FIGURE 2 Polar chart illustrating predicted screen failure rates for key safety parameters for the entire population of 3365 healthy volunteers based on common protocol defined ranges of inclusion and exclusion criteria. For each parameter, the predicted screen failure rate is shown for different protocol defined normal ranges. Applying more flexible boundaries for inclusion and exclusion criteria can markedly reduce screen failure rates and should be considered based on the risk profile of the compound. AGAH, German Association for Applied Human Pharmacology; ALT, alanine aminotransferase; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HR, heart rate; PT, prothrombin time; QTcF, corrected QT Fridericia's formula; SBP, systolic blood pressure; ULN, upper limit of normal

by selecting the most appropriate safety parameters/criteria. In addition, the results can be used to help investigator sites to optimize their screening process. The underlying dataset consisted of over 3300 unique HVs screened at a single phase I unit. Many studies report on characteristics of HVs enrolled in clinical trials, but few provide an overview of data at screening.[5,21] Yet, estimates of predicted SFR can aid in scheduling the optimal number of volunteers for screening to satisfy enrollment requirements. If screening data are available through a searchable database, this also allows targeted recruitment. As overall SFRs for phase I HV trial is up to 50%,[31–34] this could improve cost and time efficiency.

A limitation of our analysis is that SFRs were calculated for single parameters but are often interrelated (e.g., BMI with liver tests and BP), which we did not account for. In addition, we calculated SFRs as the ratio of the number of unique HVs with a value outside of the proposed range over the number of unique HVs screened for that safety parameter, which may overestimate the SFRs. The method of preselection used may significantly affect the predicted SFRs. The data derived from a single center may not be representative of HV populations at other phase I units. Finally, our recommendations to optimize the inclusion and exclusion criteria are based on clinical data related to the clinical risk of such cutoff (e.g., diastolic BP <60 mmHg) in the general population and not on a formal comparison of the safety risk during the trial of inclusion of HVs with a value of screening below or above the cutoff.

In conclusion, vital signs, ECG, and laboratory measurements are key evaluations to determine HV eligibility as they allow to detect subjects with asymptomatic underlying conditions or characteristics that may interfere with study procedures or data interpretation. Although it is clear there should never be a trade-off between safety and logistical considerations, our analysis allows for data-driven critical appraisal of commonly applied predefined protocol eligibility ranges and the safety parameters selected for inclusion and exclusion criteria. In addition, having prior knowledge on expected screen failure rates may aid investigators in organizing the screening process in the more cost- and time-efficient manner.

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CONFLICT OF INTEREST

The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

A.D. wrote the manuscript. S.L., E.M., and F.R. designed the research. A.D. and F.R. performed the research. A.D., E.C., S.L., and P.V. analyzed the data.

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