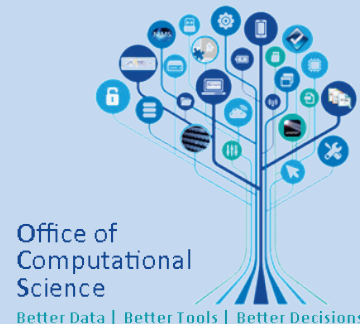


SCREEN FAILURE DATA AND SUBGROUP REPRESENTATION IN DIABETES CLINICAL TRIALS



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ABSTRACT:

FDA is mandated to report on the degree of participation and patient outcomes by racial subgroup for all new drugs approved beginning January 2015. To understand whether the extent of subgroup participation is influenced by screen failures, we reviewed trials assessed by JumpStart in 2015 and then describe the outcomes in Type 2 diabetes mellitus (T2D) clinical trials in greater detail, given the racial disparities in this therapeutic area previously reported by our group¹. Three quarters of recently submitted New Drug Applications (NDAs) assessed in JumpStart included screen failure data. Half of the studies provided the inclusion/exclusion criteria that led to designation of a screen failure, however the reason was not disclosed in >= 20% of subjects. In half of these studies, screen failure data were also submitted in the BioResearch Monitoring Program (BIMO) format specified by the Office of Compliance². Two recent NDAs for T2D did not include any SDTM screen failure data. We assessed the demographic characteristics in earlier T2D trials and describe the racial profile of subjects screened, the proportion of screen failures, and the rationale for exclusion. We found that White and Asian subjects were the most numerous of the subgroups screened and that African Americans had high rates of screen failures relative to the frequency of T2D in this racial subgroup. For example, in one NDA dataset, 68% of African Americans failed screening procedures and their final representation in the analysis population was 4%, while other race groups failed screening only 50% of the time. We will describe the inclusion and exclusion criteria that resulted in preferential screen failures. These data could help better design inclusive trials that enhance diversity in patient representation. Screen failure data are relevant to trial review, enable an insight into disproportions in subgroup inclusion, and contribute to our understanding of how these data may be better collected and evaluated in clinical trials.

BACKGROUND:

Need for Screen failure data in the review:

Screen failure data can be useful in understanding whether the study population is representative of subjects with the disease who are likely to receive therapy. It can also be helpful in managing postmarketing risks, if subjects with specific risk factors were excluded based on a screening test outcome. As well, certain subjects may be excluded because they are unable to tolerate a test dose of a new drug (e.g., inhaled formulations). The exclusion of a large number of such subjects would be useful to understand.

Screen failure data are also used by the Office of Compliance to assess study quality and data integrity at study sites, when assessing if the study is conducted according to the study protocol ³. These findings are shared with the review team and data from certain sites censored based on inspection of screen failure data quality.

Standards for electronic submission of screening data in clinical trials:

The submission of collected screening data is not specified in FDA regulations. When provided, screen failure data are located in the demographics (DM), Inclusions/Exclusion (IE), dispositions (DS) or other domains that contain protocol-specific I/E criteria. (e.g., laboratory tests in LB), highlighting the need for a standardized approach. The technical conformance guide (TCG) states that when screen failure data are provided in DM, the treatment (ARM) should be left blank. The TCG further specifies that subject level observations, be identifiable by an EPOCH, in the event that adverse reactions occur in the screening phase, as in the inhaled formulation example.

OBJECTIVE:

To characterize the reason for screen failures by race in NDAs with imbalance in racial representation relative to disease frequency in the racial subpopulation.

METHODS:

We reviewed the NDA submissions evaluated in the JumpStart service in 2015 for submission of screen failure data in the clinical trial datasets. We also screened the submission files for concurrent submission of a Bioresearch Monitoring Program (BIMO) dataset. Since we had previously described imbalanced racial representation in T2D trials, we chose to focus our description of screen failure data in trials for oral antihyperglycemic drugs.

We selected NDAs with an imbalance in the racial subgroups in the analyzed populations that also submitted screen failure data in DM and IE domains. We assessed the criteria for screen failure by evaluating nonconformance to inclusion criteria or conformance with an exclusion criteria by subject. We then summarized the reason for screen failure by racial category.

RESULTS:

Of 28 NDAs assessed through JumpStart in 2015, 22 (~78%) included screen failure records in the DM domain and 16 (57%) also contained a BIMO dataset. A total of 15 applications (~53% of NDAs) included the reason for screen failures, citing the relevant inclusion and exclusion criteria provided in the Trial Design (TD) dataset in at least 80% of subjects.

One NDA provided screen failure data from the Phase 2/3 trial pool for about 20,000 screened patients of which about 10,000 were enrolled. Nonconformance to inclusion criteria for screen failures represented 50% (n=5360) and conformance to exclusion criteria represented 50% (n=2596).

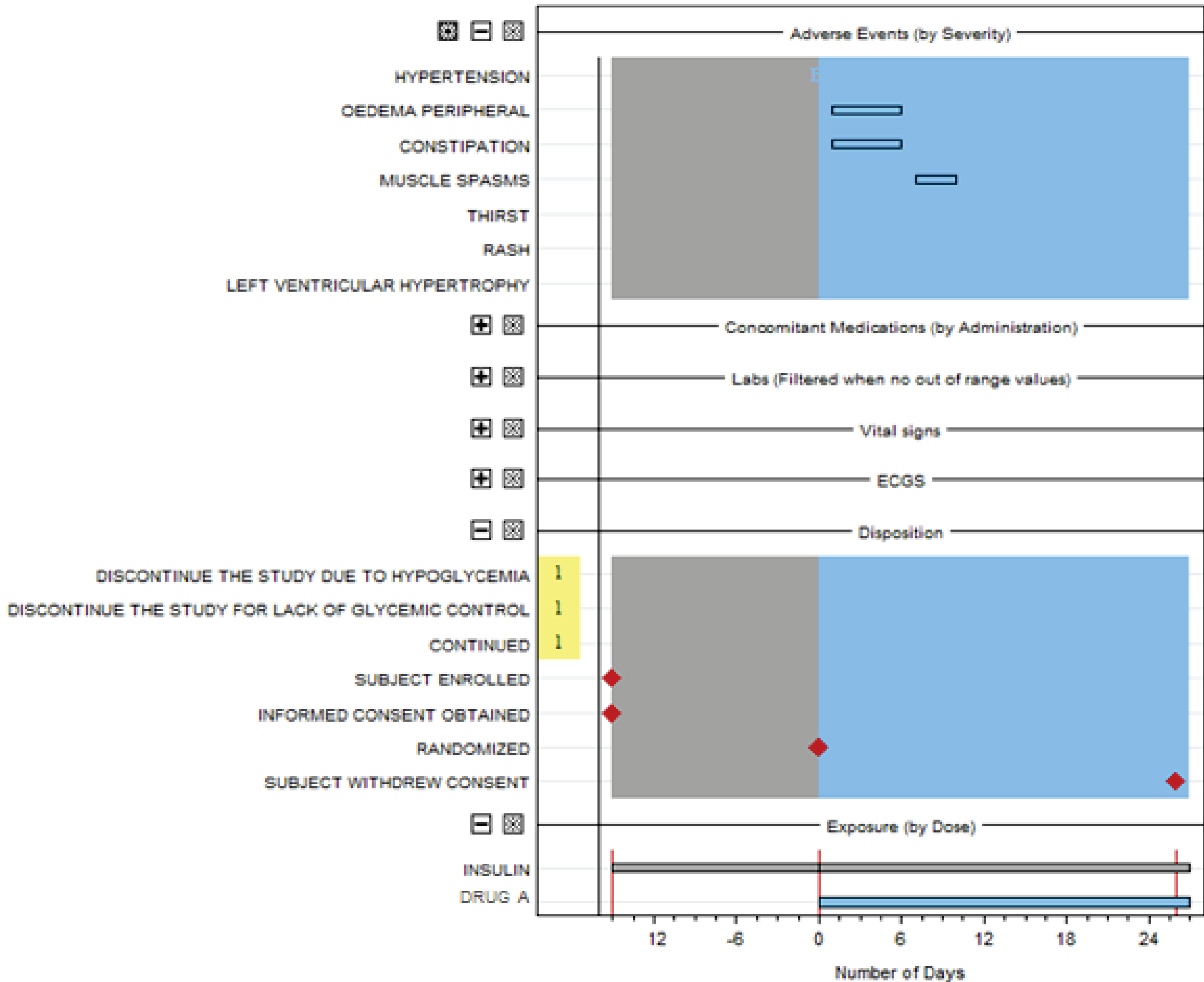
Another 25% (n=2576) did not have any data on the exclusion and inclusion criteria. The integrated dataset consisted of heterogeneous trials with a diverse array of inclusion and exclusion criteria, requiring reclassification for this presentation. For example, the following are some of the terms that were reclassified to the category of Cardiovascular Disease:

Any Of The Following Disease Within 6 Months Of Enrolment Visit: Documented History Of Myocardial Infarction; Cardiac Surgery Revascularization
Cardiovascular disease, defined as: Prior documented Coronary Heart Disease, History of myocardial infarction or History of revascularization, or coronary artery stenosis >50%, confirmed with angiography, Myocardial Infarction, Myocardial infarction, Recent Cardiovascular Events in a patient: Acute Coronary Syndrome within 2 months, etc.
Significant Cardiovascular History Within The Past 6 Months Prior To Enrolment (Myocardial Infarction, Unstable Angina, Transient Ischemic Attack (TIA), Previously Undiagnosed Arrhythmia, Significant Cardiovascular History Within The Past 6 Months Prior To The Screening Visit, Defined As: Myocardial Infarction

Inclusion and Exclusion criteria for the same concept could be further specified to reduce screening ambiguity. For example the set of criteria below does not describe how subjects who fit between the test thresholds identified in the inclusion and the exclusion criteria should be handled:

Criteria	
Inclusion	Urine Microalbumin / Creatinine Ratio < 300 Mg/G (Note also the non-standard capitalization of units in the original submission)
Exclusion	Urine Albumin:Creatinine Ratio (UACR) > 1,800 Mg/G (203.4 Mg/Mmol/Cr)

A fair amount of patients who fulfilled exclusion criteria nonetheless received treatment as documented by using a Patient Profile Viewer (See Figure)



SCREEN FAILURE CRITERIA BY RACE

Failure to conform to the inclusion criteria accounted for more screen failures that conforming to exclusion criteria. Subjects often also fulfilled more than one criteria in either category, and there were a number of subjects who were excluded on the basis of both inclusion and exclusion criteria.

INCLUSION:

Failing to meet T2D inclusion criteria was the most common reason for screen failures across all racial subgroups. Most screen failure reports due to renal inclusion criteria were in Asians, whereas Blacks had the highest CV inclusion screen failure.

Non Conformance to Inclusion Criteria by Race					
INCLUSION CATEGORIES	White	Asian/ Native Hawaiian	Black	Other	Total
Total	4059 (100%)	607 (100%)	550 (100%)	144 (100%)	5360 (100%)
DM/DKA	3313(81.62)	470 (77.43)	447 (81.27)	117 (81.25)	4347 (81.10)
Other	457 (11.26)	108 (17.79)	53 (9.64)	16 (11.11)	634 (11.83)
Cardiovascular	285 (7.02)	16 (2.64)	67 (12.18)	5 (3.47)	373 (6.96)
Renal	136 (3.35)	30 (4.94)	10 (1.82)	13 (9.03)	189 (3.53)
Investigator Pregnancy/ Contraception/ Lactation	8 (0.20)	0	1 (0.18)	0	9 (0.17)
Labs=Electrolytes	2 (0.05)	0	0	0	2 (0.04)
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Unique patients per cell
Abbreviations: CK, creatine kinase; DKA, diabetic ketoacidosis; DM, diabetes mellitus

EXCLUSION:

Renal and electrolyte criteria were a common reason for exclusion of Asian subjects. Whereas renal, hepatic, CK elevations and anemia were common causes of screen failures in blacks. In addition CK elevations and anemia were disproportionately more frequent in Blacks compared to the other subgroups. Interestingly, renal criteria was the most common cause for exclusion in the rest of the racial subgroups.

Category of Exclusion Criteria by Race					
EXCLUSION CATEGORIES	White	Asian/ Native Hawaiian	Black	Other	Total
Total	1937 (100%)	346 (100%)	235 (100%)	78 (100%)	2596 (100%)
Renal	687 (35.47)	150 (43.35)	54 (22.98)	22 (28.21)	913 (35.17)
Hepatic	361 (18.64)	77 (22.25)	52 (22.13)	23 (29.49)	513 (19.76)
Thyroid	237 (12.24)	30 (8.67)	11 (4.68)	12 (15.38)	290 (11.17)
Other	192 (9.91)	28 (8.09)	31 (13.19)	7 (8.97)	258 (9.94)
Investigator	124 (6.40)	9 (2.60)	12 (5.11)	3 (3.85)	148 (5.70)
DM/DKA	115 (5.94)	10 (2.89)	12 (5.11)	5 (6.41)	142 (5.47)
CK elevation	88 (4.54)	10 (2.89)	36 (15.32)	5 (6.41)	139 (5.35)
Electrolytes	88 (4.54)	30 (8.67)	15 (6.38)	6 (7.69)	139 (5.35)
Cardiovascular	66 (3.41)	11 (3.18)	12 (5.11)	1 (1.28)	90 (3.47)
Anemia	45 (2.32)	16 (4.62)	19 (8.09)	2 (2.56)	82 (3.16)
Pregnancy/Contraception/Lactation	14 (0.72)	9 (2.60)	1 (0.43)	0	24 (0.92)
Malignancy	21 (1.08)	0	2 (0.85)	0	23 (0.89)
Administration of any investigational drug	4 (0.21)	1 (0.29)	0	0	5 (0.19)

Unique patients per cell
Abbreviations: CK, creatine kinase; DKA, diabetic ketoacidosis; DM, diabetes mellitus

DISCUSSION:

Screen failure data are helpful in understanding the generalizability of the results from subjects who participate in clinical trials.

Underlying conditions may cause subject exclusion, such as hepatic abnormalities. Interestingly, renal disease was notable in the Asian group as an exclusion criteria.

Creatine kinase (CK) elevations in Black subjects caused more exclusions, but renal dysfunction was not disproportionate in the subgroup relative to other racial categories. It is important when possible to use the race-specific normal range for test analytes when they exist,⁴ such as for CK.

Screen failure data can help in managing post-marketing risk; an assessment of adverse events that occur in subjects who receive therapy and fail screening is necessary, as similar subjects may receive the drug when marketed.

Screening criteria can probably be modified to encourage inclusion of subjects generally excluded from these trials. In addition, pragmatic, real world trials or trials in special population may supplement the missing/limited subgroup information resulting from screen failures.

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