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Short Communication
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Unsupervised Analysis of Screen Failure Rates during Clinical Trial Enrollment Practice in a Tertiary Clinical Center of Hematology

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Abstract

Purpose: Screen Failures (SF) may occur at various rates during clinical trial enrollment, it may be difficult to pinpoint specific causes. While economic and time are the most used metrics to measure SF impact, it is to note that from a patient point-of-view these SF situations can be particularly difficult to handle. Retrospectively analyzing unenrolled patients may lead to the identification of "homogeneous" groups of patients, and help reduce SF rates.

Methods: An unsupervised dimension reduction analysis (Multiple Correspondence Analysis) on patients with SFs was conducted on a 1 year enrollment in our tertiary clinical center of hematology.

Results: Out of 232 patients deemed eligible to be enrolled, 52 patients were considered as SFs (24% SF rate). We highlight with dimension reduction that we can carve out some specific patients' profiles to be more aware of for enrollment procedures (3 main "paragons" were determined). We also noted an inflation of SF rate for patients with Lymphoid malignancies.

Conclusion: Dimension reduction may help clinical trial teams to narrow down patients that may present with a particular difficult profile to enroll.

Keywords: Clinical trial; Screen failures; Dimension reduction

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Introduction

While scrutiny is maintained by study teams and investigators, Screen Failures (SF) may arise at various stages of clinical trial enrollment, at a various rate according to trial design, and population of interest. SFs are part of clinical research and not trying to minimize their occurrence is at risk of wasting staff, time and budget. While SF's rates may vary according to the field of research, mitigation of SF rate should be thought through everyday practice. Identifying patients that may be at higher risk of SF may be among the strategies to help reduce SFs by focusing on some particularly challenging patients to enroll. Screen failure definition may be subjected to different interpretations, and while in clinical trials SF per se is limited to patients enrolled and secondly dropped-off before treatment start (e.g. after central review of an eligibility package), from a patient/physician point-of-view, SF can occur sooner, for instance after referral of the patient, by the presence of an undiagnosed prohibiting condition, existence of forbidden comedications, inadequate clinical state and/or stage of the disease. That's why we performed a comprehensive retrospective analysis of 1 year of trial enrollment in our tertiary center in order to decipher whether «homogeneous populations» of screen failures could be determined, and specifically whether phase of the trial and/or diseases could be associated with systematic biases in the rate of SF.

Methods

In order to get a precise analysis of the reasons not to perform inclusion, we prospectively collected the data of all the patients intended to be enrolled in a clinical trial from January 1st, 2021 to December 31st, 2021 (1 year). All patients were aged >18 years-old, all hematological malignancies were considered and only clinical phases I to III were included. We analyzed the disease characteristics (1L/>1L, disease category), source for referral (exterior/in-institution), phase (I/II/III), and main causes of SF (medical history, pathology, denial to enroll, logistic, competing trial). This analysis was conducted without supervision (dimension reduction analysis with multiple correspondence analysis [1], and by comparing characteristics of patients having a SF to patients

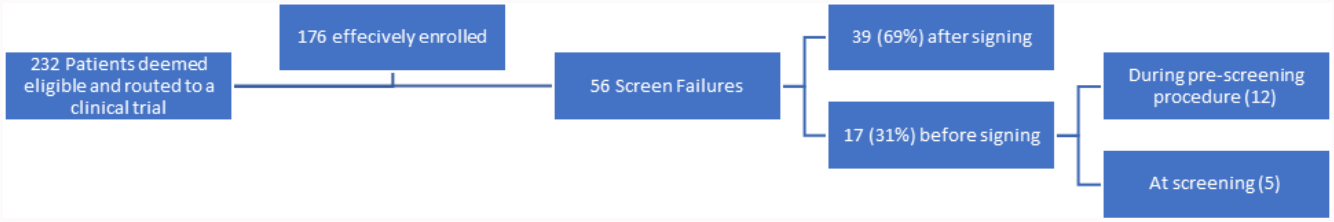

Figure 1: Consort diagram of patients deemed eligible to enroll in a clinical trial during year 2021.

without SF (Fisher test).

Results

Of 232 patients that were deemed to be enrolled in a therapeutic clinical trial, 176 (76%) were included and underwent treatment (Figure 1), hence, overall SF rate was 24%. Of the 56 patients presenting a SF, 39 patients (69%) underwent screening procedure while 17 were halted before signing (12 during a pre-screening consultation and 5 at screening consultation). Main reasons for SF were medical history (n=21, 37.5%), disease characteristics (n= 21, 37.5%), denial to enroll (n=9, 16%), logistic (n=3, 5%), competing trial (n=2, 4%).

Multiple component analysis was conducted on all the variables (except for age and sex of the patient). The first 5 components sum-up 77% of the total variance of the dataset (n=11 variables), allowing us to reliably present the results. The first plane of analysis (Axis 1&2), divided the patients in two main categories for Axis 1, having signed or not an informed consent (i.e., enrolled yes or no). The Axis-2 was associated with the presence of a competing trial, participation to phase II trial, Academic *vs.* Industrial trial or the presence of a pre-screening consultation (Figure 2).

A hierarchical ascending clustering was performed on the patient's coordinates in the 5 dimensions of the reduced space. Three main clusters of "homogeneous" profiles of patients were determined (Figure 3).

Cluster 1 was associated with patients having signed a consent,

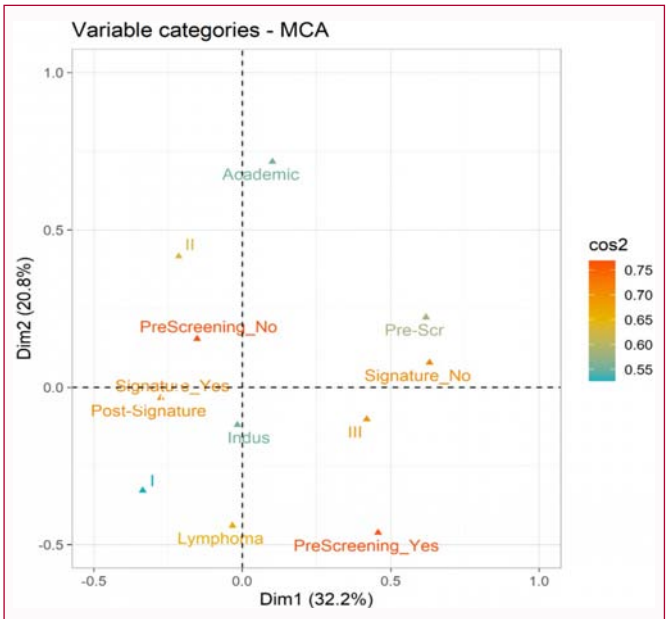

Figure 2: Variables coordinates projections on 1st plane of MCA analysis. Variables are colored according to their cos2 correlation with axis 1&2 (only variables harboring a cos2 correlation >0.55 are displayed).

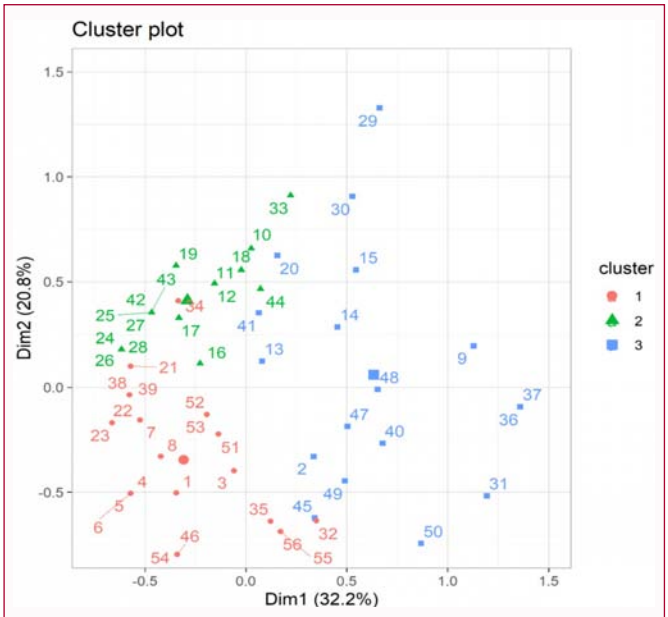

Figure 3: Subjects coordinates projection on 1st plane of MCA analysis. Ascending hierarchical clustering of the patients according to coordinates in the 5-dimension reduced space was performed. Ward distance was used to calculate distance among individual points, number of clusters was chosen as a tradeoff between informativity and homogeneity.

with a lymphoma, referred by our institution and only for Industrial trials, half of these patients were excluded from the trial because of disease characteristics and 60% of the patients were in a phase I trial. Cluster 2 was associated with phase II industrial trials involving multiple myeloma patients who had signed the consent. Finally, cluster 3 segregated patients who had not signed a consent, mostly for a phase III trial (61%), either during a pre-screening procedure or at a screening appointment, and most causes of SF were denial from the patient (Table 1).

We compared some characteristics of patients within SF cohort to determine whether some subtypes may harbor higher than expected SF rates. In particular, phases of trial (I/II/III) and disease categories were of particular interest as it may highlight some systematic biases during the screening period that may lead to an overrate of SF. Regarding trial phases, overall, no imbalance could be noted between SFs and enrolled patients (p=0.6). Regarding histological imbalance, overall testing was in favor of an imbalance (p=0.0002), when locating the difference, it appeared that there was an over-representation of lymphoid malignancies, with a SF rate of 51%, while myeloma diseases had a SF rate of 21% (p=0.001) and patients with myeloid diseases had a SF rate of 17% (p=0.0001).

Conclusion

In this analysis, we have tried to take leverage on our enrollment

Table 1: Comparison of patient's main characteristics, between patients considered in SF and patients effectively enrolled in a clinical trial.

Characteristic	SF Patients (n=56)	Enrolled Patients (n=176)	SF rate (%)
Phase			
I	16	73	18
II	18	56	24
III	22	47	32
Histology			
Myeloid	17	81	17
Myeloma	19	72	21
Lymphoid	20	19	51
Other	-	4	-

data to learn from screen failures and thus, help reduce our SF rate. We have shown that our screen failures' rate was 24% for year 2021, and that reasons for SFs were highly heterogeneous, with a majority of medical history and disease characteristics (75%), which is in line with the majority of (loosely) reported SF's rates in oncology trials [2,3]. With a joint dimension-reduction and unsupervised clustering technique we have highlighted that some patients may harbor "homogeneous" profiles, such as lymphoid patients referred by our institution for whom disease characteristics are the most common cause, or MM patients enrolled in phase II trials. Those "paragons" should be considered as red lights when preparing screening periods for those patients, with a reinforced attention. Another source of concern is dominated by Lymphoid patients, as those latter have the highest SFs rates among all patients (51%), and should benefit from a particular attention prior screening, probably with a prior pre-screening visit, that would be less burdensome in term of logistics and less costly. From a bio-economic perspective, we have estimated (data not shown) that for a large-sized French tertiary center, these SFs represent an amount of 163,000€ (medical time, technical time, logistics, etc...), and an overall 95 days of cumulative time for a single year. Finally, this kind of unsupervised analysis could be easily performed in centers, allowing them to identify particularly at-risk profiles of patients. We are prospectively analyzing our enrollment rates and failures to monitor whether such analyses should be carried on the following years and whether their impact on SFs' rate is meaningful in our practice. It is a common situation to face SF, and while a lot has been written on the medical side, one should not forget that patients often see SF as personal failures and lack of chances that should be carefully handled.

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