Automated CONSORT Flow Diagram Generation by SAS® Programming

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ABSTRACT

Consolidated Standards of Reporting Trials (CONSORT) flow diagrams are often included in the Clinical Study Report to provide a bird's eye view of the flow of patients through different stages of clinical trials. In the past these diagrams were often created manually. In this project, a SAS macro (SAS® version 9.4) is developed to automate CONSORT flow diagram generation from analysis data, ADaM ADSL (subject level analysis dataset).

The SAS macro is designed to create and display three basic elements (box, arrow and text) in the diagram by SAS SGPLOT procedure. ADaM ADSL dataset is used as the input of the macro. ADSL includes all the information needed to create the diagram. The disposition table in Clinical Study Report (CSR) is usually generated from ADSL. Using same data source will ensure consistency between CSR tables and the CONSORT diagram.

Specifically, based on ADSL and/or macro parameters specified by users, the macro will calculate/derive number of boxes needed, location and size of each box, direction of the flow from one box to another, and texts to be displayed inside each box.

Generally, the CONSORT flow diagram macro will generate boxes for screening, screen failure, enrolled (randomized), summary by treatment group and participation status at different periods of the study.
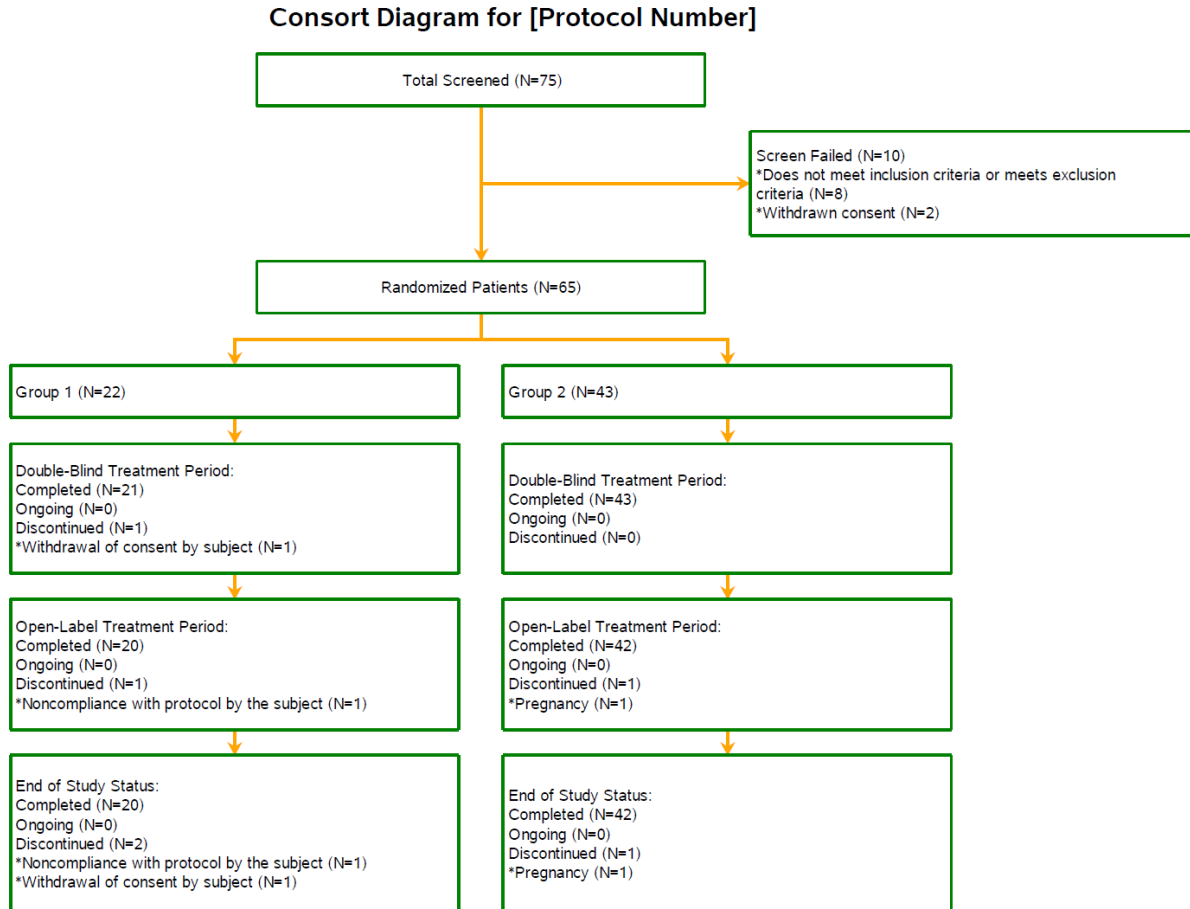
INTRODUCTION

Consolidated Standards of Reporting Trials (CONSORT) is an initiative for transparent reporting of trials came together by a group of experts in clinical trial methodology, guideline development, biomedical journal editors, and research funders. The main product of CONSORT is the CONSORT Statement, which is an evidence-based, minimum set of recommendations for reporting randomized trial. The CONSORT Statement comprises a 25-item checklist and a flow diagram. The checklist items focus on reporting how the trial was designed, analyzed, and interpreted; and the flow diagram displays the progress of all participants through the trial. The CONSORT Statement is endorsed by prominent general medical journals, many specialty medical journals, and leading editorial organizations. (CONSORT, 2010)

The CONSORT flow diagrams are often included in the Clinical Study Report to provide a bird's eye view of the flow of patients through the different stages of the trials. In the past these diagrams were created by Medical Writing group manually. Now a SAS macro is developed to automate the CONSORT flow diagram generation from analysis data, i.e. ADaM.ADSL.

The main CONSORT Statement is based on the "standard" two-group parallel design. It has been extended and modified for variations to the standard trial methodology, including different design aspects, interventions and data. (CONSORT, 2010)

There are many displays of CONSORT diagrams. We focus on including three basic components: boxes, links (between boxes) and texts (inside boxes). The format of Figure 1 has been discussed and agreed by the internal Medical Writing group.

Consort Diagram for [Protocol Number]

Total Screened (N=75)

Screen Failed (N=10)
*Does not meet inclusion criteria or meets exclusion criteria (N=8)
*Withdrawn consent (N=2)

Randomized Patients (N=65)

Group 1 (N=22)

Group 2 (N=43)

Double-Blind Treatment Period:
Completed (N=21)
Ongoing (N=0)
Discontinued (N=1)
*Withdrawal of consent by subject (N=1)

Double-Blind Treatment Period:
Completed (N=43)
Ongoing (N=0)
Discontinued (N=0)

Open-Label Treatment Period:
Completed (N=20)
Ongoing (N=0)
Discontinued (N=1)
*Noncompliance with protocol by the subject (N=1)

Open-Label Treatment Period:
Completed (N=42)
Ongoing (N=0)
Discontinued (N=1)
*Pregnancy (N=1)

End of Study Status:
Completed (N=20)
Ongoing (N=0)
Discontinued (N=2)
*Noncompliance with protocol by the subject (N=1)
*Withdrawal of consent by subject (N=1)

End of Study Status:
Completed (N=42)
Ongoing (N=0)
Discontinued (N=1)
*Pregnancy (N=1)

Figure 1.Sample Consort Diagram

The top three boxes in this example diagram displays patients count for screening, screen failure and randomization respectively. Following the randomization, patients are counted by treatment groups and participation status at the end of treatment periods (including two periods, double-blind treatment and open-label treatment) and at the end of study period.

The key elements to construct this diagram are green boxes, orange arrows and black texts.

THE SAS MACRO AND SAMPLE CALLS

INTRODUCTION OF THE SAS MACRO

The SAS macro is designed to create and display the three basic elements mentioned above by SAS SGPLOT procedure. ADaM ADSL (subject level analysis dataset) is used as the input of the macro. ADSL includes all the information needed to create the diagram. The disposition table in CSR is usually generated from ADSL. Using same data source will ensure consistency between CSR tables and the CONSORT diagram.

Based on ADSL and/or macro parameters specified by users, the macro will calculate/derive number of boxes needed, location and size of each box, direction of the flow from one box to another, and texts to be displayed inside each box.

Generally, the CONSORT flow diagram macro will generate boxes for screening, screen failure, enrolled

(randomized), summary by treatment group and participation status at different periods of the study.

GENERAL DESCRIPTION

The main macro with user interface is %gen_consort. There are three supporting macros: %makeboxes, %makelinks and %positiontext. Users do not need to interact with these supporting macros. The user guide will only focus on %gen_consort.

Macro %gen_consort takes ADSL as input dataset. Analysis Data Model Implementation Guide (ADaM IG) Version 1.1 has recommendation for commonly used variables names and labels in ADSL. For example, RANDFL (Randomized Population Flag), EOSSTT (End of Study Status), DCSREAS (Reason for Discontinuation from Study), EOTSTT (End of Treatment Status) for single treatment period, or EOT##STT for multiple treatment periods status. Macro %gen_consort is designed to use these variables as default. However, in practice, many ADSL use variable names different than the ones recommended by the ADaM IG. In addition, users can also specify the variable names through macro parameters when they are different from the ones recommended by ADaM IG.

MACRO PARAMETERS

Table 1 includes parameters currently defined in the macro %gen_consort.

Parameter	Description	Default	Example
indsn	Input dataset		indsn = ads.adsl
sfreasonn	Numeric variable to order screen failure reasons	SFREASN	sfreasonn = sfreasn Can leave null if no numeric variable in dataset
sfreasonc	Character variable for screen failure reasons	SFREAS	sfreasonc = sfeason
enrlflagname	Variable name for enrolled population flag. Values need to be 'Y' or 'N'.	Searching RANDFL or ENRLFL in input dataset. If both exist, RANDFL is preferred.	enrlflagname = RANDFL; enrlflagname = FASFL
enrlflaglabel	Text label to show in the box for enrolled population	Variable label for the searched RANDFL and ENRLFL	enrlflaglabel = Randomized Patients
trtn	Numeric variable to order subgroups	TRT01PN	trtn = sexn; trtn = trt01an
trt	Character variable for the subgroups to count patients by	TRT01P	trt = sex; trt = trt01a
eoteosname	Character variables for status at the end of treatment/study periods, separated by "|". Values need to be 'COMPLETED', 'DISCONTINUED' or 'ONGOING'.	Searching ADaM IG recommended variables for status at the end of treatment/study periods	eoteosname = EOT01STT|EOT02STT|EOSSTT
eoteoslabel	Text labels to show in the box for status at the end of treatment/study periods, separated by "|".	Labels of the searched ADaM IG recommended variables for status at the end of treatment/study periods	eoteoslabel = Double-Blind Treatment Period|Open-Label Treatment Period|End of Study Status
eoteosdiscn	Numeric variables to order discontinuation reasons at the end of treatment/study periods, separated by "|".	Searching ADaM IG recommended numeric variables for discontinuation reasons	eoteosdiscn = DCT01RSN|DCT02RSN|DCSREASN
eoteosdiscc	Character variables for discontinuation reasons at the end of treatment/study periods, separated by "|".	Searching ADaM IG recommended variables for discontinuation reasons	eoteosdiscc = DCT01RS|DCT02RS|DCSREAS
line_len	Maximum length of the text for each row. The macro calculates the length but allow users to override.	Calculated by the macro	line_len = 40

linkcolor	Color for the links between boxes	orange	linkcolor = black; When leaving it null, multiple colors are used to indicate different flows.
boxcolor	Color for the boxes border	green	boxcolor = purple
addboxlabel	Text label to show in the box for additional status after treatment/study periods, i.e., open label extension status.		addboxlabel = OLE Status
addcondlabel	Text labels to show in the box corresponding to conditions specified in addcondwhere, separated by "|".		addcondlabel = OLE|non-OLE
addcondwhere	SAS code for the conditions to count patients, separated by "|".		addcondwhere = OLEFL = 'Y'| OLEFL = 'N'
title	Title of the diagram		title = Consort Diagram for Study abc
gpath	Path to output the diagram		gpath = &studypath./Analysis_CSR/Output
filename	File name of the output diagram		filename = consort_abc
fformat	File format of the output diagram. PDF is preferred because it's editable.	pdf	fformat = pdf
dpi	Image resolution in dots per inch for the output diagram	200	dpi = 250

Table 1. Macro Parameters Description

SAMPLE MACRO CALL

This section lists some examples to show how to use the macro in different scenarios.

- Example 1:

Study 1 is a randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety. The study includes run-in/screening periods, a DBTP, a OLTP, and a follow-up period. In DBTP, patients are randomized 2:1 to receive study drug or matching placebo. And all patients receive study drug in OLTP. The following macro call generated Figure 2. Consort Diagram for .

%gen_consort(indsn = ads.adsl,

filename = consort_1,

title = Consort Diagram for Study 1,

gpath = &studypath./Output);

The ADSL for this study includes the ADaM IG recommended variables, so the macro can pick up the default variables for population flags, screen failure reason, status at the end of treatment period and study period along with discontinuation reasons from each period. It would be same to use the following call with explicit parameters specification.
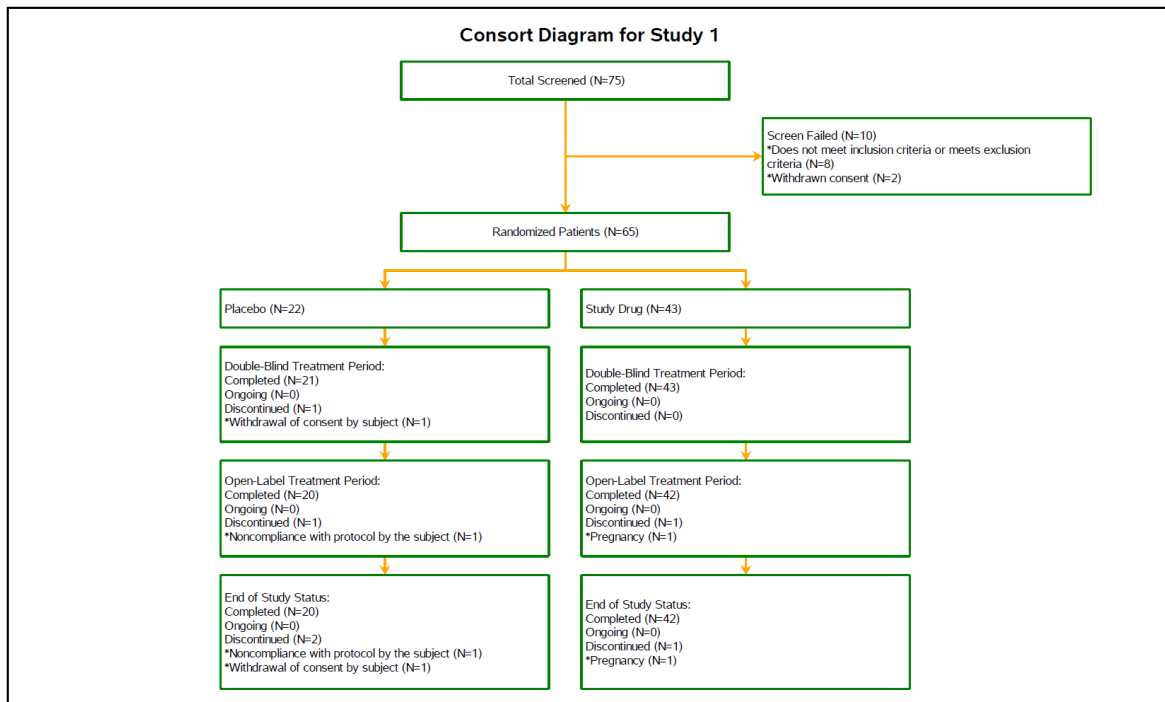
%gen_consort(indsn = ads.adsl,

filename = consort_1,

title = Consort Diagram for Study 1,

gpath = &studypath./Output,

sfreasonn = SFREASN,

sfreasonc = SFREAS,

enrlflagname = RANDFL,

enrlflaglabel = Randomized Patients,

trtn = TRT01PN,

trt = TRT01P,

eoteosname = EOT01STT|EOT02STT|EOSSTT,

eoteoslabel = Double-Blind Treatment Period|Open-Label Treatment Period|End of Study Status,

eoteosdiscn = DCT01RSN|DCT02RSN|DCSREASN,

eoteosdiscc = DCT01RS|DCT02RS|DCSREAS);

It is simpler to use the first version of macro calls, but the second version is preferred because it looks straightforward and avoid confusions by specifying values for the key parameters.

Consort Diagram for Study 1

Total Screened (N=75)

Screen Failed (N=10)
*Does not meet inclusion criteria or meets exclusion criteria (N=8)
*Withdrawn consent (N=2)

Randomized Patients (N=65)

Placebo (N=22)

Study Drug (N=43)

Double-Blind Treatment Period:
Completed (N=21)
Ongoing (N=0)
Discontinued (N=1)
*Withdrawal of consent by subject (N=1)

Double-Blind Treatment Period:
Completed (N=43)
Ongoing (N=0)
Discontinued (N=0)

Open-Label Treatment Period:
Completed (N=20)
Ongoing (N=0)
Discontinued (N=1)
*Noncompliance with protocol by the subject (N=1)

Open-Label Treatment Period:
Completed (N=42)
Ongoing (N=0)
Discontinued (N=1)
*Pregnancy (N=1)

End of Study Status:
Completed (N=20)
Ongoing (N=0)
Discontinued (N=2)
*Noncompliance with protocol by the subject (N=1)
*Withdrawal of consent by subject (N=1)

End of Study Status:
Completed (N=42)
Ongoing (N=0)
Discontinued (N=1)
*Pregnancy (N=1)
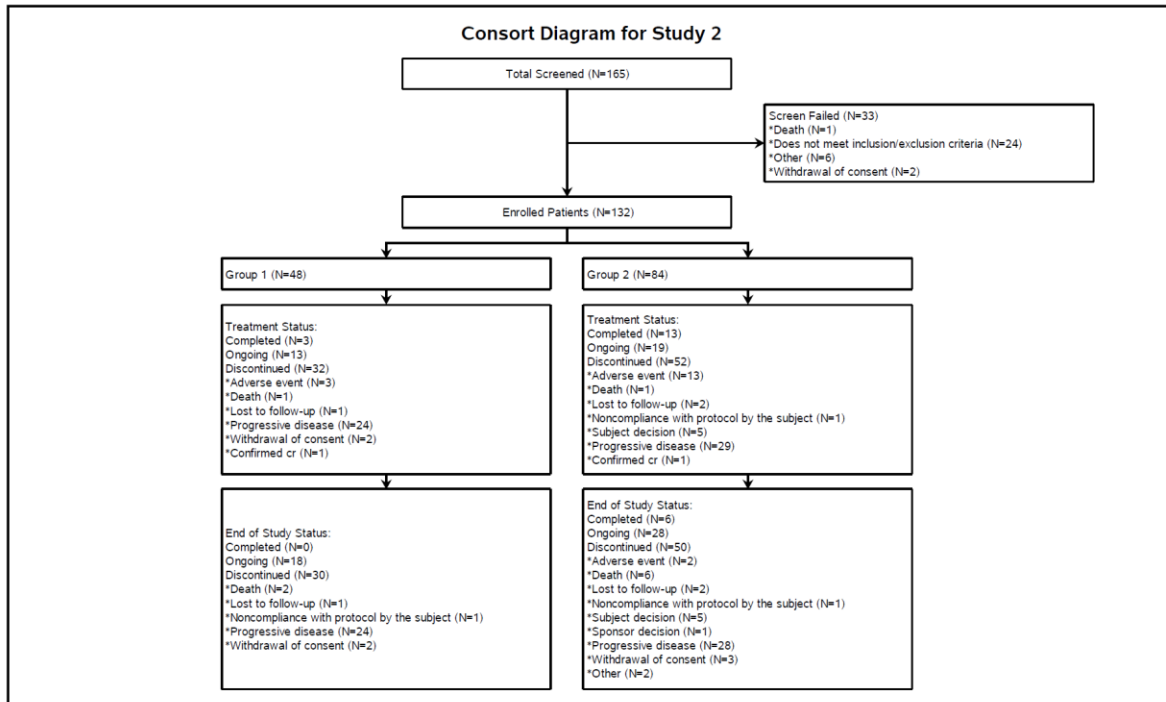
Figure 2. Consort Diagram for Study 1

- Example 2:

Study 2 is a phase 2, non-randomized, 2-group, multi-center study. The study will have 2 groups. Group 1 and Group 2.

The study includes a screening period, a treatment period, and a follow up period. The following macro call generated Figure 3. Consort Diagram for Study 2.

%gen_consort(indsn = ads.adsl,

        filename = consort_2,

        title = Consort Diagram for Study 2,

        gpath = &studypath./Output,

        sfreasonn = ,

        sfreasonc = SFREA,

        enrlflagname = ENRLFL,

        enrlflaglabel = Enrolled Patients,

        trtn = TRT01PN,

        trt = TRT01P,

        eoteosname = EOT01STT|EOSSTT,

        eoteoslabel = Treatment Status|End of Study Status,

        eoteosdiscn = DCT01RSN|DCSREASN,

        eoteosdiscc = DCT01RS|DCSREAS,

        line_len = 55,

        linkcolor = black,

        boxcolor = black);

This sample call shows ENRLFL is used to indicate the eligible patients in this study. This ADSL does not include a numeric variable to order screen failure reasons, so parameter *sfreasonn* is left null. The order of screen failure reasons displayed in the box will be based on the character variable. In addition, there is only one treatment period in this study so parameter *eoteosname* includes two variables, the first one for status at the end of treatment period and the second for end of study period. Correspondingly, parameters *eoteoslabel, eoteosdiscn* and *eoteosdiscc* all have two values separated by "|". Parameter *line_len* is used for a better text split than default. Users usually need to try a few different values to find the optimal one. At the end, black color is specified for both links and boxes border.

Consort Diagram for Study 2

Total Screened (N=165)

Screen Failed (N=33)
*Death (N=1)
*Does not meet inclusion/exclusion criteria (N=24)
*Other (N=6)
*Withdrawal of consent (N=2)

Enrolled Patients (N=132)

Group 1 (N=48)

Group 2 (N=84)

Treatment Status:
Completed (N=3)
Ongoing (N=13)
Discontinued (N=32)
*Adverse event (N=3)
*Death (N=1)
*Lost to follow-up (N=1)
*Progressive disease (N=24)
*Withdrawal of consent (N=2)
*Confirmed cr (N=1)

Treatment Status:
Completed (N=13)
Ongoing (N=19)
Discontinued (N=52)
*Adverse event (N=13)
*Death (N=1)
*Lost to follow-up (N=2)
*Noncompliance with protocol by the subject (N=1)
*Subject decision (N=5)
*Progressive disease (N=29)
*Confirmed cr (N=1)

End of Study Status:
Completed (N=0)
Ongoing (N=18)
Discontinued (N=30)
*Death (N=2)
*Lost to follow-up (N=1)
*Noncompliance with protocol by the subject (N=1)
*Progressive disease (N=24)
*Withdrawal of consent (N=2)

End of Study Status:
Completed (N=6)
Ongoing (N=28)
Discontinued (N=50)
*Adverse event (N=2)
*Death (N=6)
*Lost to follow-up (N=2)
*Noncompliance with protocol by the subject (N=1)
*Subject decision (N=5)
*Sponsor decision (N=1)
*Progressive disease (N=28)
*Withdrawal of consent (N=3)
*Other (N=2)

Figure 3. Consort Diagram for Study 2

- Example 3

Study 3 is a randomized, double-blind, placebo-controlled study. The study includes a screening period, a treatment period and a follow up period. In treatment period, patients are randomized in a 1:1:1 ratio to treatment group 1, treatment group 2, treatment group 3 or placebo.

All patients will be offered the opportunity to screen for entry into the OLE study at the end of the treatment period. The following macro call generated Figure 4. Consort Diagram for Study 3Study 3.

%gen_consort(indsn = adsl,

  filename = consort_3,

  title = Consort Diagram for Study 3,

  sfreasonn =,

  sfreasonc = SFREAS,

  enrlflagname = RANDFL,

  enrlflaglabel = Randomized Patients,

  trtn = TRT01PN,

  trt = TRT01P,

  eoteosname = EOTSTT|EOSSTT,

  eoteoslabel = Treatment Status|End of Study Status,

  eoteosdiscn = EOTRSNN|EOSRSNN,

  eoteosdiscc = EOTRSN|EOSRSN,

8

```
line_len = 40,

linkcolor =,

boxcolor = black,

addboxlabel = OLE Status,

addcondlabel = OLE|non-OLE,

addcondwhere = ole = 1| ole ^= 1);
```

In this study, the ADSL includes variables CMPTRTFL and COMPLFL for status at the end of treatment and study respectively. However, the values of these two variables are 'Y' or 'N'. The macro requires that the values need to be 'COMPLETED', 'DISCONTINUED' or 'ONGOING'. Therefore, two variables, EOTSTT and EOSSTT for treatment and study periods status, were derived in an intermediate data step and later used in the macro.

In addition, this sample macro call specifies values for parameters *addboxlabel*, *addcondlabel* and *addcondwhere*. This set of parameters work together to display an extra set of boxes after end of study status, which shows patient counts by participating open-label extension study or not. When *linkcolor* is not specified, it will vary by different flows.
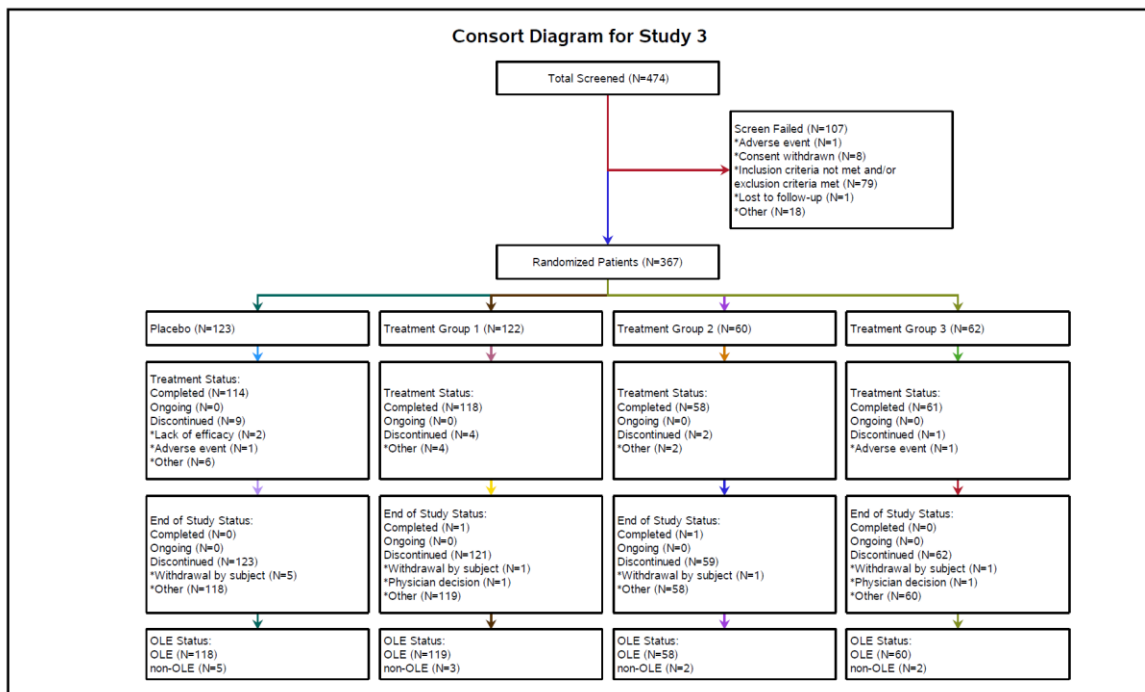
Figure 4. Consort Diagram for Study 3

CONCLUSION

This paper introduces a SAS® macro to automate CONSORT diagram generation. Since the layout of the diagram such as box location, box size, links between boxes and texts, is automatically arranged in the macro, it significantly reduces manual efforts spent on the

diagram. The input source of the macro is ADSL, which is the same source as used to create disposition CSR table, ensures the consistency.

REFERENCES

COSORT 2010

http://www.consort-statement.org/

SESUG Paper 271-2018 CONSORT Diagrams in SGPLOT: Adding Efficiencies

https://www.lexjansen.com/sesug/2018/SESUG2018_Paper-271_Final_PDF.pdf

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