NONMEM Users Guide - Part III

NONMEM 7.5.0 Installation Guide

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by

Robert J. Bauer

Alison J. Boeckmann

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PREFACE

The NONMEM Installation Guide contains more details on NONMEM installation than are needed by most users. If NONMEM is to be installed under Microsoft Windows/MS-DOS or Unix/Linux/OS X, look first at the README_750 document on the CD. It describes an easy installation using SETUP75.BAT (for Windows/MS-DOS) and SETUP75 (for Unix/Linux/OS X).

All files are distributed on a single CD.   There is no single-precision version of NONMEM 7. You must replace all of NONMEM, PREDPP, and NM-TRAN. Do not mix new and old versions of the various components of the NONMEM system!

The MS-DOS installation utility is now called SETUP75.BAT. The UNIX installation utility is called SETUP75. UNIX shell scripts NMFE75 and MS-DOS batch file NMFE75.BAT are used to run NONMEM 7.5. They both have an option "recompile" that allows the source code to be recompiled easily after a change to SIZES.

There is a single INCLUDE file named SIZES.f90. This file contains all the constants pertaining to NM-TRAN, NONMEM, and PREDPP. Many of the constants can be changed with the $SIZES record in a control stream file, although still some require modification in SIZES.f90, and recompilation of the NM-TRAN and NONMEM system.

When re-running old NONMEM problems, please be aware of the following facts:

NONMEM output changes slightly with each version.

It is possible that the results of the Estimation and Covariance Steps may be different than with earlier versions of NONMEM.

Old Model Specification files (MSF's) *cannot* be re-used with a new release.

Old F77 Fortran subroutines (e.g., PRED, MODEL, PK, DES, AES routines) (whether user-coded or generated by NM-TRAN) *cannot* be re-used without certain modifications into F90 format.

Old NM-TRAN control streams and NM-TRAN data files can be re-used. Old NONMEM data files can be re-used.

In general, we have tried to make NONMEM 7.5 upwards compatible from earlier versions of NONMEM 7.

In the hardcopy and pdf versions of this guide, significant changes to the content versus the NONMEM 7.4 have been made. The appropriate citation to use for the NONMEM software and these guides is:

Beal SL, Sheiner LB, Boeckmann AJ, and Bauer RJ (eds) NONMEM 7.5 Users Guides. (1989–2020). ICON plc, Gaithersburg, MD. https://nonmem.iconplc.com/nonmem750

Chapter I - Introduction

1. How to Use This Guide

This guide describes how to install and test the NONMEM system, which consists of NM-TRAN, NONMEM, and PREDPP Version 7.5. The NONMEM system is distributed as FORTRAN 95 source code. There is only one version of NONMEM 7.5; this guide tells how to modify the installation in order to customize it for your computer and your operating system.

The first chapter describes system and compiler requirements and discusses certain decisions that must be made before installation begins. Later chapters give step by step instructions for installing the major components of the system, testing them, and running them.

Please follow these steps when installing the NONMEM system:

1. Read this Users Guide III. It describes the various components of the NONMEM system and how they are used. Please familiarize yourself with the components of the NONMEM system and how they relate to each other.
2. Review decisions. The people who will use NONMEM should be consulted on these decisions.
3. Follow the instructions on installation.
4. If any questions or persistent problems arise regarding installation, please send electronic mail to: nmconsult@iconplc.com.
5. You may also ask questions of other NONMEM users by way of the NONMEM Users Network, described in Section 6.

Please do not make ANY changes to the source code other than the ones described in this guide without first talking to the NONMEM consultant. Unless such changes are approved, the NONMEM consultant cannot help you with problems which may arise. The NONMEM consultant is familiar with the problems you will encounter during the installation, and will be able to suggest the best fix for your situation.

2. System Requirements

2.1. Memory Requirements (RAM)

The size of a NONMEM executable ("load module") varies considerably, depending on which optional routines are included. However, all modern computers can run NONMEM 7 easily.

2.2. Compiler Requirements

The compiler must implement the ANSI FORTRAN 95 standard. The Essential Lahey Fortran 90 Compiler does **not** support the complete Fortran 95 standard and is **not** suitable for use with NONMEM, although other Lahey Fortran compilers can be used.   In addition the compiler must implement certain other features:

1.   It must allow the default length of integer variables to be 4 bytes. *All subroutines must be compiled with the default length of integer variables as 4 bytes*.

2.   It must allow variables of different types to share the same storage area using the EQUIVALENCE statement.

3.   It is desirable that floating point underflow be permitted to occur silently, but *only* if the resulting value is set to zero; this is the default action specified by the IEEE 754 standard for floating point arithmetic.

4.   It must allow the FORTRAN INCLUDE statement. It is part of the FORTRAN 95 language. If your system does not permit INCLUDE statements, please contact the NONMEM consultant.

NONMEM 7.5 has been successfully compiled using the following compilers:
1)   Intel Fortran 8.0 and higher, for Windows, MAC OSX, or Linux
2)   GNU gfortran version 4.6.0 for Windows, or version 4.4.0 20090219 Trunc version 144289 for Linux.
3)   GNU gfortran version 4.6.3 for Windows for Linux.
4)   GNU fortran version 4.8.5 for Linux or Windows
5)   Catalina 10.15 MAC OS X, gfortran 9.2

2.3. Speed Requirements

NONMEM run times vary greatly, depending on the amount of data and the complexity of the model. Extensive use is made of floating point arithmetic, so it is necessary to have a floating point (math) processor. With most modern machines, simple problems with moderate size population data sets, such as are used in the various examples in the Users Guide, will run in a reasonable amount of time (no more than an hour, often much less). With more complicated problems, run times can be as much as 10 hours or more. Machines with speeds of 1 GHz or more are preferred.

Prior to installing NONMEM a test of your compiler is appropriate to assure that your compiler

is properly configured. An example of such a test is given in the Installation Chapter IV.

2.4. Disk Space Requirements

The NONMEM system is read from the NONMEM distribution medium in the form of encrypted FORTRAN 95 source code. Chapter II describes the number of bytes of storage required for each file on the medium. On most systems, the compiled object code (binary code) occupies more disk space than does the original source code. In general, at least 400 MB of disk storage are desirable during the installation of NONMEM. Additional storage will be needed for the user files: input data files, output reports, etc.

3. Additional Documentation

All other volumes of the NONMEM Users Guide should be available for reference as needed during the installation process. In particular, examples of input and output to be used as test cases during the installation are found in NONMEM Users Guide, Parts I and VI. The inputs are recorded on the distribution medium. The results files can be found at
https://nonmem.iconplc.com/nonmem750/STDResults/
The additional documentation is listed in section 2.5

Emails and Technical Newsletters

From time to time, emails and technical newsletters are sent to all current NONMEM licensees. These may give hints and suggestions on the installation and use of the system. Please be sure to review all emails and technical newsletters, if any, that accompany the NONMEM distribution medium. If you think you may be missing relevant newsletters, please call the NONMEM consultant.

See also Section 7 of this chapter for a list of internet sites from which bug memos and fixes may be obtained.

5. A Few Remarks about the Examples

In the following chapters, complete examples of operating system commands and features are given for two commonly used operating systems: UNIX (specifically, Ubuntu Linux), and MS-DOS (specifically, an MS-DOS window running under Microsoft Windows XP, using Intel Fortran 9.0 and higher). MS-DOS examples can also be used with Microsoft Windows 7 and Vista.

The UNIX examples all use commands for the Bourne shell.

Only UNIX and MS-DOS examples are included because these are the only operating systems with which we have first hand experience. NONMEM has been installed under a variety of other operating systems.

The examples, suitably modified for local differences, may suffice for many users. For other operating systems, they may be helpful as samples of what can be done. For example, NONMEM 7.5 has been installed on a MacBook Pro running OS X using the UNIX/Linux installation instructions.

People who are proficient in the use of their local operating system may well choose to do things

differently.

6. The NONMEM Users Network

You and the NONMEM users at your site are invited to participate in the NONMEM Users Network. It is an electronic mailing list, not a news group. A user with a question, remark, or discussion which he believes might interest or help other NONMEM users sends the item to a single e-mail address. The item is automatically broadcast to every e-mail address on the network. The mail is not reviewed by anyone before it is broadcast. The NONMEM Users Network helps users worldwide communicate with each other, share information, and solve problems. In addition, technical newsletters describing bug fixes may be sent via e-mail to the network, as well as by ordinary (paper) mail to all licensees.

To be added to the mailing list (or to be removed from it), please send a request containing your e-mail address to:
nmusers-request@iconplc.com.

Thereafter, to send an item to the network, send it to:
nmusers@globomaxnm.com.

You may send questions to the network even if you are not actually on the mailing list, but be sure to include your e-mail address for replies.

7. Internet Sites

Bug lists may be found at the following sites:

https://nonmem.iconplc.com/nonmem750/nm750_bug_list.pdf
https://nonmem.iconplc.com/nonmem744/nm744_bug_list.pdf
https://nonmem.iconplc.com/nonmem743/nm743_bug_list.pdf
https://nonmem.iconplc.com/nonmem742/nm742_bug_list.pdf
https://nonmem.iconplc.com/nonmem741/nm741_bug_list.pdf
https://nonmem.iconplc.com/nonmem740/nm740_bug_list.pdf
https://nonmem.iconplc.com/nonmem730/nm730_bug_list.pdf
https://nonmem.iconplc.com/nonmem720/nm720_bug_list.pdf
https://nonmem.iconplc.com/nonmem712/nm712_bug_list.pdf
https://nonmem.iconplc.com/nonmem710/nonmem_7.1.0_bug_List_5_NOV_2009.pdf
https://nonmem.iconplc.com/nonmem/NONMEM_VI_buglist
https://nonmem.iconplc.com/nonmem/NONMEM_V_buglist

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Chapter II - How to Read the NONMEM Distribution Medium

This chapter describes the contents of NONMEM distribution medium, and describes how to read the files.

1. Media Characteristics

NONMEM source code, On-line Help files, and Users Guides are distributed on a single CD.

Only one version of NONMEM is distributed. Changes to the source code should not be required to specialize it to a particular computer system.

2. Contents of the Distribution Medium

2.1. Top Directory

These files provide scripts and executables that are needed for installing NONMEM in several environments.

```
BuildEnvironmentWindowforNONMEM.pdf
install_Darwin
install_Darwin_32
install_darwin_32.txt
install_Darwin_powerpc
install_Linux
install_SunOS
install_SunOS_i386
install_Win.exe
intro7.pdf (same as nm750.pdf)
NONMEM-PDx-Pop-Support.pdf
nonmem.lic
readme_750.pdf
SETUP75
SETUP75.bat
unzip.exe
unzip.SunOS
```

2.2. compilers

Compilers are no longer distributed with the NONMEM distribution medium, but are located on:

https://nonmem.iconplc.com/nonmem7/compilers/

Further information about compilers can be found in readme_750.pdf

2.3. mpich2

Installers for mpich2 are no longer on the distribution medium, but can be found at

https://nonmem.iconplc.com/mpich2

In addition, materials for installing Microsoft MPI for Windows are located at:

https://nonmem.iconplc.com/msmpi

Further information about MPI can be found in readme_750.pdf.

2.4. NONMEM_7.5.x

```
guides.zip
help.zip
html.zip
nonmem75e.zip
nonmem75r.zip
```

2.5. guides.zip

The zip file guides.zip contains all parts of the NONMEM Users Guide as PDF files. These files may be searched and displayed on-line. They may also be printed.

Name of Documentation	Description/Title
I.pdf	Users Basic Guide A step by step discussion of various NONMEM features and statistical concepts involved in using NONMEM. Of historical interest for early versions of NONMEM. Part V should be read first.
II.pdf	Users Supplemental Guide A continuation of Part I which includes some special features of NONMEM.
III.pdf	NONMEM 7.5 Installation Guide
IV.pdf	NM-TRAN Guide A complete reference guide to NM-TRAN (which includes the Data Preprocessor).
V.pdf	Introductory Guide A guide for beginning users of NM-TRAN/NONMEM-PREDPP. A NONMEM user should read the Introductory Guide first.
VI.pdf	PREDPP Guide A complete reference guide to PREDPP.
VII.pdf	Conditional Estimation Methods A description of these methods and some guidelines for their use.
VIII.pdf	Help Guide A fast way to locate information on a given word or topic. The content of the Help Guide is also supplied on the NONMEM distribution medium for on-line use.

Name of Documentation	Description/Title
nm750.pdf (intro7.pdf)	Introduction To Nonmem 7.5.0 Describes changes from NONMEM VI Release 2.0, to 7.1.0, 7.1.2, 7.2.0, 7.3.0, 7.4.1, 7.4.2, 7.4.3, 7.4.4, and 7.5.0.
Supp.pdf	NONMEM V Supplemental Guide Describes changes found with NONMEM V of which the user should be aware, especially if he used earlier versions of NONMEM.
Intro.pdf	Introduction to Version VI Describes changes and new features found with NONMEM VI of which the user should be aware, especially if he used earlier versions of NONMEM.
Readme_750.pdf	NONMEM750 Release Memo The NONMEM Distribution medium contains files readme_750.pdf (The names may change with future releases.) The ".pdf" file may be viewed with Adobe Acrobat Reader;. You may print it. Their content is identical with chapter IV of this installation guide. The "readme" contains important information that was developed too late for inclusion in this guide. Be sure to read it.
Nonmem7_technical_guide.pdf	Technical Guide on the Expectation-Maximization Population and Monte Carlo Analysis Methods in the NONMEM 7 Program
cvs_guide.pdf	Guide on CVODES (ADVAN14)
cv_guide.pdf	Guide on CVODE (ADVAN14)
idas_guide.pdf	Guide on IDAS (ADVAN15)
ida_guide.pdf	Guide on IDA (ADVAN15)
Manrad5-v2.pdf	Guide on RADAR5 (ADVAN16, ADVAN17)
Ddes_f90.pdf	Guide on DDE_SOLVER (ADVAN18)

2.6. help.zip

This zip file contains help files for the console help system. The file helptools.zip contains files that is useful with on-line help files in the MS-DOS platform.

2.7. html.zip
This zip file contains files for the help system that can be navigated using an internet browser such as Windows Internet Explorer.

3. Storage of the Distribution Medium

Once the source code has been read, the CD (if you acquired one) should be stored in a safe place for subsequent use. If you erase the source code from disk after installation, you will have to read it back from the original medium to make corrections or changes. If at some future time you wish to transfer NONMEM to a different computer, you should re-install it from the original medium. If you terminate your NONMEM license, you must destroy all computer files containing NONMEM system source, binary code, and derivative products, and return the medium to the distributor, ICON Plc Development Solutions.

Chapter III - The New Features and Bug Fixes of NONMEM 7.5 compared to NONMEM 7.4.0

New features and bugs fixes from previous version to NONMEM 7.5 are listed in section I.1 of guides\intro7.pdf

Chapter IV - How to Install and Test NONMEM

The detailed instructions for installing and testing NONMEM are located in readme_750.pdf.

Chapter V – Modification of Execution

1.0. Version Identification

NONMEM is an evolving program, and changes are made from time to time. Version and level numbers together identify a particular instance of NONMEM. The first line of a NONMEM output report gives version and level numbers. These numbers identify the instance of NONMEM used to generate the output. As a result of implementing bug fixes that are announced in an email or newsletter, the level number is automatically changed.

In SIZES.f90 there is a level number given in a DATA statement similar to the follow-ing:

```
MODULE VERSION
CHARACTER(LEN=80)    :: LEV
DATA LEV/'7.5.0'/ ! Version No.
END MODULE VERSION
```

Do not change this version number.

2.0. Bug Fixes in NONMEM 7.5

Bug fixes to NONMEM 7.5 will be issued to nmusers, and uploaded to
https://nonmem.iconplc.com/nonmem750/nm750_bug_list.pdf

3.0. SIZES

Certain constants are used by NONMEM to control array and buffer sizes, and may be changed by the user, many of them by using the $SIZES record in their control stream file.

For permanent changes, values may be changed in SIZES.f90. Values that are changed in SIZES.f90 take affect after all the appropriate NONMEM source modules have been recompiled and, if a binary library is used, after the binary library has been rebuilt. Note that PREDPP and NM-TRAN Routines also use constants from SIZES. If you change a constant in SIZES, comments will tell you if other components of the NONMEM system should be recompiled.

Several of the constants in SIZES are of special interest.

3.1. Changing the Number of Theta's, Eta's, and Epsilon's

LTH gives the maximum number of theta's allowable.
LVR2 controls the maximum number of eta's permitted when the Laplacian Method is used.

The values in SIZES on the distribution medium are as follows.

```
  PARAMETER (LTH=100)
  PARAMETER (LVR=30)
  PARAMETER (LVR2=20)
```

NM-TRAN dynamically sizes LTH and LVR for you, which can be over-ridden by the user, by

inserting the following line in the beginning of the control stream file, for example:
```
$SIZES LTH=150 LVR=60 LVR2=60
```

Constants LTH, LVR, and LVR2 may also be permanently increased in SIZES.f90, but you should not decrease them.

3.2. Increasing the Number of Observations per Individual Record

As of NONMEM 7.3, the maximum number of observations for a given individual is assessed by NMTRAN. It is possible that the calculation may be inadequate. If this constant is not adequate, NONMEM will produce an error message such as the following.

```
 TOT. NO. OF OBSERVATIONS IN INDIVIDUAL REC NO.    1 (IN INDIVIDUAL REC
 ORDERING)
EXCEEDS  250
```

To increase this limit, add the following record as the first executable line in the control stream file:

```
$SIZES NO=500
```

And re-run the problem again.

3.3. Changing the Size of Common NMPRD4 (LNP4)

Common NMPRD4 is used for communication between NONMEM and the PRED subroutine (and also for communication between user-supplied routines for PREDPP). To change its size, specifiy in the control stream file,

```
$SIZES LNP4=5000
```

Or some other appropriate. Typically, users who write abbreviated code will consider making this change only when the following error message is produced by NM-TRAN:

```
288   SIZE OF NMPRD4 EXCEEDED; LNP4 IS TOO SMALL IN NMTRAN AND NONMEM
```

When abbreviated code is not used, positions in NMPRD4 are assigned explicitly in user-supplied code. Users can determine for themselves if the common area is too small for their needs.

3.4. Changing the Size of NONMEM Buffers (LIMxx)

See Changing the Size of NONMEM Buffers in Introduction to NONMEM 7.5, nm750.pdf.

3.5. Increasing the Number of Mixture Models

Should NMTRAN fail to provide a sufficient size for number of mixture models, the size can be changed, by inserting the following line at the beginning of the control stream file:

```
$SIZES MMX=15
```

Change the value MMX to the desired value.

3.6. Increasing the Number of Individual Records in the Data Set

See Changing the Size of NONMEM Buffers in Introduction to NONMEM 7.5, nm750.pdf.

3.7. Increasing the Max. No. of Points of Support with Nonparametric Estimate

With the Nonparametric method ($NONPARAMETRIC), the points of support are the posthoc estimates of each eta, which is essentially equal to the number of individuals in the data set. (An individual record has a value of the ID data item that is different from that of the previous individual record.)

This limit is set by constant LSUPP. If this constant is not adequate, NONMEM will produce an error message such as the following.

```
NONPARAMETRIC  ESTIMATE  NOT  OBTAINABLE  WHEN  NO.  OF  INDIVIDUALS

EXCEEDS 4050
```

Change the value LSUPP to the desired value.

```
$SIZES LSUPP=6000
```

4.0. Modifying System Action in the Event of Floating Point Exceptions

Floating point arithmetic (e.g., division by zero, overflow, or underflow) sometimes occur during a NONMEM run. See Users Guide V, Chapter 13, Section 4.5. The ANSI FORTRAN 95 standard does not specify what should happen when a floating point exception occurs. Consequently, each operating system and compiler takes a different action, ranging from an immediate abort of the program to continuation with no warning that such an event occurred. Some systems, however, permit the user to control the situation. We recommend that installers check the FORTRAN Users Guide or equivalent documentation for their system and learn how to give their users some means of controlling the actions taken by their system.

It is always safe to ignore floating point underflow, *provided* that the resulting value is set to zero; this is the default action specified by the IEEE 754 standard for floating point arithmetic. For other error conditions, the run should stop and produce as much diagnostic information as possible when an error occurs. so that the cause of the errors can be investigated. Second, if the user concludes that the errors are benign and are unavoidable, it should be possible for him to cause the errors to be ignored.

See Section 2.1.3 for code that can be used with Sun FORTRAN compilers.

With some compilers, a compiler option can be used to specify how floating point exceptions are handled. For example, with Intel Visual Fortran, we suggest the option

```
/fpe:0
```

With Sun FORTRAN, we suggest

```
-fnonstd
```

These options request that the program stop if floating-point overflow, division by zero, or an invalid operation exception occurs. With Sun, the message "illegal instruction" appears. Both also request that underflow to zero occur for excessively tiny quantities.

If the compiler produces fatal error messages, or if you are concerned about warning messages, contact the NONMEM consultant. Do not attempt to fix the source code yourself! Phone at (301) 944-6807 or send e-mail to nmconsult@iconplc.com.

5.0. NONMEM Routines CRIT, MIX, PRIOR, CONTR, CCONTR, CONSTRAINT, USMETA, SPTWO

These are NONMEM dummy routines ("stubs") that may be replaced by user-written subroutines. Specify the name of the routine on the $SUBROUTINES record, as in this example.

```
$SUBROUTINES .... MIX=subname ...
```

NM-TRAN opens the file named "subname" and copies it to FSUBS.

Similarly, if the $MIX block of abbreviated code is present, then a generated code for MIX is present in FSUBS, or, if NM-TRAN Library routines are used, the NM-TRAN Library MIX routine must be included in the NONMEM executable.

Because NONMEM routines are obtained from a binary library (nonmem.a or nonmem.lib), the linker uses the MIX subroutine in FSUBS (or the NM-TRAN library) rather than the MIX routine from NONMEM.

6.0. PREDPP Routines, INFN, TRANS

These are PREDPP routines that may be replaced by user-written subroutines. Again, this is done by specifying the name of the routine on the $SUBROUTINES record, as in this example.

$SUBROUTINES .... INFN=subname

NM-TRAN opens the file named "subname" and copies it to FSUBS. The information in FREPORT causes NMLINK6 to omit PREDPP's INFN routine from the list of files in LINK.LNK.

7.0. User Utility Routines

User-supplied routines and NM-TRAN verbatim code may contain calls to other user-supplied subroutines, which are referred to as *user utility routines*. Such routines may be included in the NONMEM executable module. First, they may be listed as OTHER routines on the $SUBROUTINES record, as in this example.

$SUBROUTINES .... OTHER=BSPLINE

NM-TRAN opens the file named "BSPLINE" and copies it to FSUBS. It is compiled and included in the NONMEM executable.

A second way permits pre-compiled routines or libraries to be included automatically. The OTHER option is not used. Instead, the nmfe75 shell script or nmfe75.bat batch file should be modified. Locate the line u= or set u=, respectively.

Two examples of how this line might be changed are given for UNIX, and two examples are given for MS-DOS:

UNIX:
```
set u="/.../.../mylib.a"
```
MSDOS:
```
Set u=BSPLINES.obj
set u="\...\...\mylib.lib"
```

In the first examples, an object module BSPLINE is included in the NONMEM executable whether or not it is used in a given run. In the second example, "/.../.../mylib.a" stands for the full path of a binary library. Modules from this library are included only if actually called. In both nmfe75 and nmfe75.bat, the order presented to the linker is: nonmem library followed by user library or modules ($n $u in UNIX and %n% %u% in MS-DOS). As a result, the user utility routines cannot themselves call NONMEM utility routines such as CHOL or SUPP. If they do call NONMEM routines, the order must be reversed ($u $n in UNIX and %u% %n% in MS-DOS). This must be done with care because a routine in a user library having the same name as a NONMEM routine will be used instead of the NONMEM routine.

8.0. User Supplied Routines

Users may choose to substitute their own subroutines for certain default NONMEM-PREDPP routines, as follows:

NONMEM routines: CRIT, MIX, PRIOR, CONTR, CCONTR, CONSTRAINT, USMETA, SPTWO.

PREDPP routines: INFN and TRANS.

Users may also supply their own complete PK, ERROR, MODEL, DES, and AES sub-routines, rather than use NM-TRAN abbreviated code ($PK, etc.). They may also supply a TOL subroutine rather than supply a value on the $SUBROUTINES record.

NONMEM and PREDPP should be installed in such a manner that substitutions are possible.

Substitutions are specified to NM-TRAN on the $SUBROUTINES record. For example, if a user-supplied MIX routine is used with file name MIXUSER, the option MIX=MIXUSER appears on the $SUBROUTINES record. NM-TRAN uses such information in two ways:

Substitutions are documented in the FREPORT file, which contains a complete description of the composition of the NONMEM-PREDPP executable.
All user-supplied subroutines are copied to file FSUBS, to help in the construction of the actual executable.

9.0. User Files

A user might supply a subroutine that requires I/O. FORTRAN logical units in the range 51-2000 may be used. If user files are output, it can be important to close them properly before the NONMEM run terminates. Use of the NONMEM utility FILES can help perform this function.

10.0. The Files Utility

Whenever a FORTRAN OPEN statement or a CLOSE statement is executed in a user-supplied routine, NONMEM should be informed. This should be done as follows. Immediately after the OPEN or CLOSE statement is executed, a call should be issued to a NONMEM utility subroutine called FILES. The form of the call is simply:

```
 CALL FILES (IUNIT)
```

where IUNIT is the number of the logical unit involved in the OPEN or CLOSE statement. When this is done, if a file is open when NONMEM terminates, the file is properly closed.

If reads or writes are issued to a given unit, but no OPEN statement for this unit is exe-cuted, then when ICALL is 0, a call to FILES should be issued (before any I/O statement.

11.0. NM-TRAN Include Lines

The NM-TRAN control file may contain one or more lines of the form

INCLUDE filename
The file with name "filename" is an *NM-TRAN include file*. NMTRAN opens the include file, reads it to end-of-file and includes its contents in place of the INCLUDE record. The contents of the include file may be any portion of an NM-TRAN control stream: control records and/or abbreviated code.

12.0. Uninstalling NONMEM 7

NONMEM may be uninstalled with the following DOS command
rmdir /q /s nonmemdir

or unix command:
rm –r nonmemdir

Chapter VI - Other Files on the Distribution Medium

This chapter discusses the remaining files on the distribution medium.

1. Files for Installation Tests

In Chapters III, IV and V, we recommend that you try simple test cases after installing each component of the NONMEM system. The files necessary for these tests are printed in other Users Guides, and are also provided on the distribution medium. These files are located in the util directory of the installed nonmem directory:

PRED1 - PRED subroutine for Chapter III (NONMEM)
     Printed as Figure 1 in NONMEM Users Guide I.

CONTROL1 - Control file for Chapter III (NONMEM)
     Printed as Figure 2 in NONMEM Users Guide I.

PK1 - PK subroutine for Chapter IV (PREDPP)
     Printed as Figure 7 in NONMEM Users Guide VI.

ERROR1 - ERROR subroutine for Chapter IV (PREDPP)
     Printed as Figure 11 in NONMEM Users Guide VI.

CONTROL2 - Control file for Chapter IV (PREDPP)
     Printed as Figure 25 in NONMEM Users Guide VI.

CONTROL3 - Control file for Chapter V (NM-TRAN)
     Printed in Appendix IX in NONMEM Users Guide IV.

DATA3 - Data file for Chapter V (NM-TRAN)
Printed in Appendix IX in NONMEM Users Guide IV.

2. Phenobarbital and Theophylline Data Files

PHENO - Phenobarbital Data
     This is the complete data for the Phenobarbital example used in NONMEM Users Guide V (Introductory), Chapters II and XI. The record length is 80 bytes. There are 745 lines in the file.

THEO - Theophylline Data for PRED
     This is the theophylline data for the first illustrative run of Chapter I, Section 2.5 of this guide, which uses PRED abbreviated code, not PREDPP. The data are printed in Users Guide IV, Appendix II. The record length is 80 bytes. There are 132 lines in the file.

THEOPP - Theophylline Data for PREDPP
     This is the theophylline data for the second, third, and fourth illustrative runs of Chapter I, Section 2.5, of this guide, which use PREDPP. The data are printed in NONMEM Users Guide IV, Appendix VI. The record length is 80 bytes. There are 144 lines in the file. Note that the data of THEO are identical to that of THEOPP, except that each subject's dose amount is recorded separately from his first plasma concentration, as required with PREDPP.

3. NM-TRAN Control Streams for Illustrative Runs

CONTROL4 - Theophylline control file: PRED abbreviated code

This is a double precision version of the the NM-TRAN control stream for the first illustrative run of Chapter I, Section 2.5, of this guide. The contents of the file is printed in Users Guide IV, Chapter I. The data of file "THEO" should be used with this control stream.

CONTROL5 - Theophylline control file: PREDPP with ADVAN2

This is a double precision version of the NM-TRAN control stream for the second illustrative run of Chapter I, Section 2.5. The contents of the file is printed in Users Guide IV, Chapter V.

The data of file "THEOPP" should be used with this control stream. It produces essentially the same result as the first illustrative run, but uses PREDPP and the One Compartment Model with First Order Absorption (ADVAN2).

CONTROL6 - Theophylline control file: PREDPP with ADVAN7

This is a double precision version of the NM-TRAN control stream for the third illustrative run of Chapter I, Section 2.5. The contents of the file is printed in Users Guide IV, Appendix VIII. The data of file "THEOPP" should be used with this control stream. It produces essentially the same result as the second illustrative run, but uses PREDPP and the General Linear Method with Real Eigenvalues (ADVAN7). Normally, one would not use ADVAN7 when it is possible to use ADVAN2 because of the increased run time, but this is done here to provide an illustration of comparative executable sizes and run times.

CONTROL7 - Theophylline control file: PREDPP with ADVAN6

This is a double precision version of the NM-TRAN control stream for the fourth illustrative run of Chapter I, Section 2.5. The contents of the file is printed in Users Guide IV, Appendix VIII. The data of file "THEOPP" should be used with this control stream. It produces essentially the same result as the second illustrative run, but uses the General Non-Linear Kinetics Method (ADVAN6). Normally, one would not use ADVAN6 when it is possible to use ADVAN2 because of the increased run time, but this is done here to provide an illustration of comparative executable sizes and run times.

4. Example Control Stream Files

Additional control stream files are located in the examples directory. Accompanying them are standard NONMEM result files, with which you may compare with your run. These examples are described in Introduction to NONMEM 7.5 guide.

Chapter VII - NONMEM Users Guide and On-line Help

This chapter discusses documentation that can be found on the NONMEM distribution medium.

1.0. PDF Guides

The guides directory contains all parts of the NONMEM Users Guide as
PDF files. These files may be searched and displayed on-line. They may
also be printed.

Name of Documentation	Description/Title
I.pdf	Users Basic Guide
II.pdf	Users Supplemental Guide
III.pdf	NONMEM 7.5 Installation Guide
IV.pdf	NM-TRAN Guide
V.pdf	Introductory Guide
VI.pdf	PREDPP Guide
VII.pdf	Conditional Estimation Methods
VIII.pdf	Help Guide
nm750.pdf	Introduction To Nonmem 7.5.0
Supp.pdf	NONMEM V Supplemental Guide
Intro.pdf	Introduction to Version VI
Nonmem7_technical_guide.pdf	Technical Guide on the Expectation-Maximization Population and Monte Carlo Analysis Methods in the NONMEM 7 Program
cvs_guide.pdf	Guide on CVODES (ADVAN14)
cv_guide.pdf	Guide on CVODE (ADVAN14)
idas_guide.pdf	Guide on IDAS (ADVAN15)
ida_guide.pdf	Guide on IDA (ADVAN15)

2. On-line Help

Directories help and html contain the same material that is distributed as pdf files NONMEM Users Guide Part I- Part VIII, Help Guide. In addition, they contain files that enable the material to be searched and displayed conveniently when installed on a computer. When installed as suggested, they implement the *On-line Help* feature of NONMEM. Their installation and use is optional.

2.1. HTML help

The HTML versions work with all web browsers such as Internet Explorer, Netscape, Firefox, etc., and can be used with all operating systems. As of NONMEM VI 2.0, the html directories contain sub-directories I, II, III, etc, containing NONMEM Users Guides I, II, III, etc. in html format. These are provided so that references between and within Users Guides can be followed by the browser as hyperlinks. This feature is not fully implemented.

Start a web browser such as Internet Explorer, Netscape, or Firefox. On the File menu, you should find a button called Open or Open File. Type (or browse for) the directory, e.g., c:\nm750\html or /export/home/nm750/html. Type the file name index.htm (not $index.htm). This should open a page with the title
This is the main index of Hyper-NMhelp.

You may find it convenient to bookmark the page.

The use of Hyper-NMhelp is straightforward. Note that the keywords may be grouped somewhat differently than they are with the command-line on-line help described in the following sections.

2.2 COMMAND-LINE HELP (nmhelp)

Help files are intended for command-line usage, and may be useful when working from a UNIX or MS-DOS command prompt, or if there is no web browser available. Dos_tools allow convenient command-line help under MS-DOS. Users with other operating systems can use the command-line Help material, but they may have to create their own user-interface for search and display; the UNIX and MS-DOS examples may serve as convenient starting points.

The Help Guides consists of two sections: an index, which is printed in two parts (RESERVED WORDS and MISCELLANEOUS TOPICS); and over 200 individual discussions, which are also printed in two parts (DETAILED DESCRIPTIONS and EXAMPLES). In the Help directory, a file named index contains both parts of the printed index, in a format designed for use by the UNIX and DOS tools included on the distribution medium. Also on the Help Guide directory are over 200 files with names of the form xxxx.xxx, each of which contains the text of a single individual discussion. These files are referred to collectively as "detailed description files" in the examples below. (The suffix identifies the content. For example, examples have names ending with the suffix exa.)

If you opted to have the help manual installed when you ran SETUP75, then the nonmem directory (such as c:\nm750\help or /export/home/nm750/help) will contain the console/command line help system, nmhelp. The nmhelp file is either a DOS executable (nmhelp.exe), or a Unix bash script (nmhelp).

To use the nmhelp system in DOS, you must be in the help directory,
```
cd c:\nm750\help
```
Then select a topic, such as:
```
nmhelp ADVAN9
```

To use the nmhelp system in unix,
```
cd ~/nm750/help
```
Then select a topic, such as:
```
./nmhelp ADVAN9
```

In unix, you may execute nmhelp from any directory if you do the following. Insert the following line into your login file, such as the file .bashrc in your user directory:
```
alias nmhelp=~/nm750/help/nmhelp
```

or whatever directory your nonmem directory is located. Then, you may enter
```
nmhelp
```
from any directory.

To get information on the command nmhelp itself, enter "nmhelp help"

To get a list of the topics available, enter "nmhelp".

To get information on a given reserved word or topic, enter "nmhelp" followed by the reserved word or topic. For example,

```
nmhelp nonlinear

Help for nonlinear is available in the following documents:
1 ADVAN10                   4 NONMEM model
2 ADVAN6 ADVAN8             5 NONMEM program
3 ADVAN9                    6 Michaelis Menten example

Your choices:
enter "p number" to print a document (e.g., p1 or p 1)
enter the number of the document you wish to see
enter <CR> to see document number 1
enter q <CR> to quit this list
```

A number 1 through 6 may be entered, and the appropriate document will be displayed at the terminal. You may then enter a different number to display a different document.

2.3. Information about the DOS Tools Components (nmhelp.exe)

nmhelp.exe
A compiled C-program that searches for and displays detailed description documents. It must be used on a 386-based DOS system or higher. It uses utility programs from the Free Software Foundation.

nmhelp.c

The source code for nmhelp, in case it is necessary to re-compile it on your system. A C or C++ compiler will be required if you choose to modify the code and create a new nmhelp.exe by running nmhelp_win.bat; we do not provide it.
gawk.exe, grep.exe

Compiled utility programs from the Free Software Foundation. Must be used on a 386-based DOS system or higher.
Other files in the Dos_tools directory are gnulic.txt (a license agreement from the Free Software Foundation which should be read by anyone who wishes to make the utilities available to others).

2.4. Using nmhelp with Ordinary MS-DOS commands

Here is a very rudimentary way to search and display the   contents   of the Help Guide, using ordinary DOS commands. A better way involves the use of nmhelp, described in the previous section.

Change to the directory into which you read the Help files.

To get information on a given reserved word or topic, enter "find" followed by the reserved word or topic in quotes (""). For example,

```
find "nonlinear" index

---------- INDEX
advan10.ppp˜ ADVAN10˜ nonlinear kinetics model
advan68.ppp˜ ADVAN6 ADVAN8˜ general nonlinear kinetics model advan68.ppp˜
ADVAN6 ADVAN8˜ nonlinear kinetics model advan9.ppp˜ ADVAN9˜ general
nonlinear kinetics model advan9.ppp˜ ADVAN9˜ nonlinear kinetics model
nonmod.gen˜ NONMEM model˜ nonmem nonlinear mixed effects model nonpro.gen˜
NONMEM program˜ nonmem nonlinear mixed effects model michaeli.exa˜ Michaelis
Menten example˜ nonlinear kinetics model
```

The first column lists detailed description files. The second column gives their titles. The third column gives the context in which the search word "nonlinear" appears as a keyword in these files. (The column delimiter is the character ˜).

To display a document in the list, enter "more" followed by the filename. For example,

```
more < advan10.ppp
```