RELEASE NOTES

NONMEM 7.4.1

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Table of Contents

I. Description of Changes from NONMEM 7.3.0 to NONMEM 7.4.1

New Features of NONMEM 7.4 Compared to NONMEM 7.3.
The main new features of NONMEM 7.4 compared to NONMEM 7.3 are described in detail in Introduction to NONMEM 7.4.1 nm741.pdf, Section I.1.

The upgrade of NONMEM 7.4.1 from NONMEM 7.4.0 consisted of the following bug fix:

14.0 When a non-random variable (one not associated with etas or epsilons) is introduced within an IF/THEN block, and utilized in a nested IF/THEN block or later used outside the block, the parsing of user code into intermediate variables by NMTRAN occurs incorrectly and can result in incorrect evaluations based on that non-random variable. For example, in the following code:

```
…
IF (AGE.GE.16) THEN
   SCRMM=SCR*10/MWTCR
   IF (SCRMM.GE.0.06) THEN
      CLCR=0.516*(112-AGE)/(112-40)*FSEX/SCRMM
   ELSE
      CLCR=0.516*(119-AGE)/(119-40)*FCPR/SCRMM
   ENDIF
ENDIF
…
```

The non-random variable SCRMM is introduced in the above IF/THEN block, and then used in the subsequent IF/THEN block. The result is an incorrect assessment of 0 for SCRMM, and a value of Infinity for CLCR. A work-around for this is to initialize the non-random variable unconditionally outside of all IF/THEN blocks:

```
…
SCRMM=0.0
IF (AGE.GE.16) THEN
   SCRMM=SCR*10/MWTCR
   IF (SCRMM.GE.0.06) THEN
      CLCR=0.516*(112-AGE)/(112-40)*FSEX/SCRMM
   ELSE
      CLCR=0.516*(119-AGE)/(119-40)*FCPR/SCRMM
   ENDIF
ENDIF
…
```

This bug has been fixed in NONMEM 7.4.1.

Downloading the NONMEM7.4.1 CD Image from ICON's NONMEM ftp site.
You may download the CD image as a zip file from

https://nonmem.iconplc.com/nonmem741

Once downloaded, unzip the file (password is obtained from IDSSOFTWARE@iconplc.com), making sure options to extract sub-directories and use of folder names are turned on.

A directory called c:\nm741CD should be produced (or wherever you decided to place the directory). Then execute the SETUP74 script to install nm74. Specific instructions for Windows are found in IV.6, and for Linux, Mac or Solaris system are found in section IV.7, below.

In addition to this document, you may also consult NONMEM Users Guide III, which has some additional information about installing NONMEM 7.4. Please note that the parallelization procedure introduced in NONMEM 7.2 has not changed. For convenience, notes on parallelization are still included in these release notes, although they are not a new item. Therefore, if you already have protocols established for parallelization, including an MPI system, these do not have to be re-installed. However, if you had made specific changes to SETUP74 (such as compiler options), or nmfe74, then comparable changes will need to be made to SETUP74, or nmfe74. Also, wherever 74 or 7.3.0 was used in your specialized scripts, you may need to change these to 74 or 7.4.1, etc. Once NONMEM is installed, the name of the execution script for NONMEM 7.4 is nmfe74 (Linux) or nmfe74.bat (Windows).

II. Documentation Changes of NONMEM 7.4.1

The examples, help, html, and pdf guides III, IV, V, VI, and VIII have been updated for NONMEM 7.4.1. The proper citation for the NONMEM software and its documents is

Beal SL, Sheiner LB, Boeckmann AJ, and Bauer RJ (eds) NONMEM 7.4 Users Guides. (1989–2017). ICON plc, Gaithersburg, MD. https://nonmem.iconplc.com/nonmem741

Components	Version Number
NMTRAN	7.4.1
PREDPP	7.4.1
NONMEM	7.4.1

III. Bugs Fixed from NONMEM 7.3.0 to NONMEM 7.4

The bugs that have been detected in NONMEM 7.3, and have been fixed for NONMEM 7.4 are listed in the **Bugs Fixed** portion of Section 1.1 of nm741.pdf.

IV. NONMEM_7.4.1 Installation: Getting Started

These notes describe some fairly quick ways to install NONMEM. In particular, these notes cover:

Installation on a Windows system from a CD-ROM or directory

Installation on a UNIX or Linux or Mac OS X system from a CD-ROM or directory

Compiler test for Windows systems

Additional Mac OS X issues

Installation of NONMEM_7.4.1 is very similar to that of NONMEM_7.3.0. To install NONMEM, a FORTRAN compiler must already have been installed on your system. Parts of NONMEM 7.4.1 are provided as unencrypted source code, which can be modified by the user, and other parts are encrypted and cannot be directly accessed or modified by the user. Two "SETUP" scripts, SETUP74.bat and SETUP74, are currently available, the first for Windows and the second for Linux, Unix, and Mac OS X. These scripts are used to install NONMEM with ifort (Intel Fortran 90/95), gfortran or g95. If you use g95, it is recommended that the latest version from ftp.g95.org be used, especially with Mac OS X or Linux. However, g95 has not been tested extensively with NONMEM 7.4.1, and may not be able to compile the routines needed for parallel processing with the MPI method. Furthermore, g95 compiled NONMEM programs are known to execute very slowly, and among the free compilers, GNU gfortran is preferred. Recent versions of gfortran are available at http://gcc.gnu.org/wiki/GFortranBinaries and are in the compilers directory of the CD. See also Section IV Additional software for compilers.

SETUP74.bat and SETUP74 include a default designation ifort for the FORTRAN compiler. However, the "default compiler" may not be the one that has been installed on your system. Please acquaint yourself with which FORTRAN compiler has been installed, and perhaps more importantly, with the command name that designates this compiler. Then if this compiler is not the default compiler and/or its designation is not the default designation, you can override the default designation. System environmental variables associated with the compiler should be set before proceeding. Please see the documentation for your compiler and the document on the NONMEM distribution CD-ROM, NONMEM-PDx-Pop-Support.pdf, that contains information on how to set the system environment variables via the Windows Control Panel. The BuildEnvironmentWindowforNONMEM.pdf provides additional information on setting up environment variables for installation with the Intel Fortran compiler on Windows. See also section IV.10 on how to set the environment variables just during the period of NONMEM execution using nmloc.

IV.1 HELP Files

The command-line nmhelp utility for Windows has been improved. It is still possible that nmhelp.exe does not work on all versions of Windows at this time. Niclas Jonsson has given us permission to include the html files produced by nmhelp2html. SETUP74.bat and SETUP74 will copy this directory to the NONMEM 7.4.1 installation directory. To access this help facility double click on the index.htm (not $index.htm) file. If you detect a problem in using the html files, please report this to us.

IV.2 License File

A license file named nonmem.lic is included on the CD. However, it will expire after some time. The contact person for the license should contact ICON Development Solutions via e-mail IDSSOFTWARE@iconplc.com requesting a new license and providing the name of the licensee (company and department or individual). A new nonmem.lic file with an expiration date corresponding to the next license renewal date will be sent by return e-mail.

IV.3 Free MPI software

Directory mpich2 of the nm741CD contains a number of files that implement
MPI-2.2, the Message Passing Interface (MPI) method of parallel processing.
The contents of this directory is discussed in the **Parallel Computing**
Section of Introduction to NONMEM 7.4.1 (nm741.pdf, available in the guides directory after installation of NONMEM).
Note that MPICH2 need not be installed if parallel processing is not used, as will be the case with the typical single-CPU single-core installation of NONMEM. SETUP74 does not copy the directory to the nm741 directory. The installer material (zip file, unzipped contents, or CD) should be retained in case this directory is to be used in the future.

IV.4 Free Compilers

Directory compilers of the nm741CD contain the following files:
gcc-trunk-i686.tar.gz (gfortran for Linux)
gfortran-windows-460.exe (gfortran 4.6.0 for Windows)
gfortran-4.5.0-x86_64-SnowLeopard.dmg (gfortran 4.5.0 for Mac OS X 10.6)
gfortran-macosx-x86.dmg   (gfortran 4.5.0 for Mac OS X 10.5)

Same as the files with the same names on the web site. See below.

The ftp folder,   https://nonmem.iconplc.com/nonmem7/compilers , contains free compilers available under public license that have been found to work correctly with NONMEM 7. The compilers currently available in the directory are listed below. Please read the associated license agreements after installation of the compiler and comply appropriately with the stated requirements.

"gfortran-windows.exe" is a GNU gfortran compiler (version 4.5.0) that may be used on 64-bit versions of Microsoft Windows (e.g. Vista 64-bit) as well as 32-bit versions. It requires the user to manually create an appropriate LIBRARY_PATH environment variable after installing the compiler. The file was originally obtained from http://gcc.gnu.org/wiki/GFortranBinaries.

"gfortran-windows-460.exe" is not the latest GNU gfortran compiler (version 4.6.0) but has been tested for NONMEM 7.4.1.

"gcc-trunk-i686.tar.gz" is a GNU gfortran compiler (version 4.4.0) that may be used on 32-bit versions of Linux operating systems. The file "GFortranBinaries32Linux - GCC Wiki.mht" found in this directory contains information regarding the installation of this compiler. The file was originally obtained from http://gcc.gnu.org/wiki/GFortranBinaries.

"gfortran-4.5.0-x86_64-SnowLeopard.dmg" is a GNU gfortran compiler (version 4.5.0) that may be used on 64-bit Mac OS X such as 10.6 (Snow Leopard). Click on the file or type   the command "open 4.5.0-x86_64-SnowLeopard.dmg" to install.
The file was originally obtained from http://gcc.gnu.org/wiki/GFortranBinaries.

"gfortran-macosx-x86.dmg" is a GNU gfortran compiler (version 4.5.0) that may be used on 32-bit versions of the Mac OS X such as 10.5 (Leopard). Click on the file or type the command "open gfortran-macosx-x86.dmg" to install. The version we provide (from 2009) is difficult to find on the web as of current writing (2010) because web sites such as gcc.gnu.org have packaged the Snow Leopard version under the older name. If you installed gfortran 4.5.0 and cannot run it because it is the wrong architecture, uninstall it with command
"sudo rm -r /usr/local/bin/gfortran /usr/local/gfortran /Library/Receipts/gfortran.pkg"

As more compilers are tested they will be added to the ftp folder as a convenience for NONMEM users. It is the responsibility of the user to read and comply with all GNU license requirements.

Keep in mind that the free compilers undergo frequent modifications.   It is the user's responsibility to choose a version that works properly with NONMEM 7.

Note that installing from a dmg on a Mac may be done by clicking on the dmg file in finder, or by opening a terminal window and typing the commands "cd Downloads; open ……dmg".
The user may have to change the Apple menu "System Preferences, Security and Privacy, Allow apps downloaded from:" to allow "App Store and identified developers." Click "OK" on an alert box during the install itself to allow gfortran.pkg to be opened from an unidentified developer. It may also be necessary to go back to Security and Privacy and click on "Open Anyway".

Instructions for gfortran on macOS Sierra Version 10.12
Install the command line developer tools (see IV.9.1 Missing Unix commands) if this has not been done already.

Apple-style installers for macOS may be found at
http://gcc.gnu.org/wiki/GFortranBinaries.
Click on MacOS.
You will find a list such as the following:

macOS Sierra (10.12): download gfortran 6.3
OS X El Capitan (10.11): download gfortran 6.1
OS X Yosemite (10.10): download gfortran 5.2 or gfortran 4.9.2
OS X Mavericks (10.9): download gfortran 4.9.0 or gfortran 4.8.2
OS X Mountain Lion (10.8): download gfortran 4.8.2
OS X Lion (10.7): download gfortran 4.8.2
Detailed instructions can be found here.

Click on "download gfortran 6.3" to download **gfortran-6.3-Sierra.dmg**
Install this like any dmg (see above). Be sure to click open and read README.html,
and to install the corresponding command-line tools by typing the command

xcode-select --install

Users who installed NONMEM before upgrading to Sierra from a previous release of MacOS
may find that gfortran versions such as 5.2 and 6.1 continue to work after the upgrade and there
is no need to re-install gfortran or NONMEM. To learn what version of gfortran you are using,
type the command
gfortran --version.
You should receive several lines of text, including something like:
GNU Fortran (GCC) 6.3.0

If gfortran fails after the upgrade and needs to be reinstalled, the following command will
remove the previous version:
sudo rm –r /usr/local/gfortran /usr/local/bin/gfortran
Now try re-installing gfortran as above.

Regardless of the approach that you use to install gfortran, it is necessary that the $PATH
environment variable knows the location of gfortran. It is usually installed in /usr/local/gfortran.
However, it is symbolically linked to/usr/local/bin/gfortran (and /usr/local/bin is almost always
in $PATH). Sometimes the command "rehash" may be needed to make sure $PATH is up to
date.

Now NONMEM must be reinstalled with the new gfortran, using the SETUP74 command.

An error message such as the following may occur during the NONMEM install if the command-
line tools are not the correct versions:
util/test.c:1:19: fatal error: stdio.h: No such file or
directory
Be sure to type xcode-select as above.

Additional Comments: The name suggested for the NONMEM 7.4.1 installation directory, nm741, may be changed. E.g., if this directory already exists and contains a pre-release version of NONMEM, then one should use a name such as nm741_1.0 instead. Directories (c:\nm741 and /Users/Shared/nm741) are only suggestions. In previous versions of this guide, /opt was suggested rather than /Users/Shared. With Mac OS, /Users/Shared is preferable because it avoids the need for root permission when NONMEM is installed. Or install in the user's home directory $HOME/nm741, which is suggested below. Other directories may be used in a server-type installation.

With NONMEM 7.1, the SETUP command offered a choice for sizes ("reg", "big", "same"). Beginning with NONMEM 7.2, this choice is ignored. It is in effect always "same and is shown as "same" in all examples. However, some constants in SIZES are not dynamically allocated (for example, LSTEXT; see help entry for sizes). To change such a constant, stop the installation (or reinstallation) at the point where SETUP74 pauses with the message
"Changes to License file, resource/SIZES.f90 and other resource files may be made here."
In the target directory (e.g., `C:\nm741\resource`), edit SIZES.f90 (be sure to copy the original as a backup), and retype the SETUP74 command as before. Use option "rec" (recompile) rather than "norec".

IV.5 Note on Parallelization

When using Intel Fortran compiler 11.1 or 12.0, the results of an FOCE analysis may differ slightly when running in single CPU mode versus parallel processing mode, but the results should still be very similar in well posed problems. Adding the compiler switch /O1 may make the results between single CPI and parallel processing more consistent, although NONMEM runs may execute more slowly. To add this switch, insert /O1 after Ob1gyti in SETUP74.bat (line 245), or –O1 in SETUP74 (lines 381,384). Then use the appropriate SETUP74 script for installation. Should this still result in slightly different results between single CPI and parallel processing mode, try the following compiler options in place of the ones that are in the SETUP74 scripts:
For SETUP74:
-fp-model strict -Gs -nologo -nbs -w
For SETUP74.bat:
/fp:strict /Gs /nologo /nbs /w

Note that all examples of commands are to be typed on one line, even though they may appear to be split between two lines. The SETUP command should be run in the foreground, not the background.

IV.6 Installation on a Windows system from a CD-ROM or Directory

Easy Install:

If you are content to use a pre-supplied gfortran compiler, then the following easy install method is suitable for most Windows users.

Easy installers for NONMEM 7.4.1

Please visit the site at
https://nonmem.iconplc.com/nonmem741

And download one of the following, and follow the instructions:

Windows 7 64 bit Easy Install:
Installer:
NONMEM741_64gfortran463.exe

installation instructions:
Download NONMEM741_64gfortran463.exe

Once downloaded, run the program (start->run, or run from a dos window).
Obtain password from IDSSOFTWARE@iconplc.com
Answer questions.

After installation, there should be a nm74g64 icon on your desktop. Click on
it, and a command window will open.

The program has an expired license file.   Therefore, copy your up-to-date license file
nonmem.lic to the directory
\nm74g64\license
This needs to be done only once.

Then execute the test problem
nmfe74 control5 control5.txt -prdefault

The objective function should be about 104.56

This version has its own gfortran with a built-in path to it, and is designed to be run from any command window.

There is no need to run the SETUP74 script.

If you are using PDxPop5, then run PDxPop5 and in the configuration section,
"Tools > Edit Configuration insert c:\nm74g64 as the NONMEM directory, and
GFORTRAN as the compiler.

Windows XP 32 bit Easy Install
Installer:

NONMEM741_gfortran460.exe

installation instructions:
Download nonmem741_gfortran460.exe

Once downloaded, run the program (start->run, or run from a dos window).
Obtain password from IDSSOFTWARE@iconplc.com
Answer questions.

After installation, there should be a nm74g ICON on your desktop. Click on
it, and a command window will open.

The program has expired license file. Therefore, copy your up-to-date license
file nonmem.lic to the directory
\nm74g\license
This needs to be done only once.

Then execute the test problem
nmfe74 control5 control5.txt -prdefault

The objective function should be about 104.56

This version has its own gfortran with a built-in path to it, and is designed to be run from any
command window.

There is no need to run the SETUP74 script.

If you are using PDxPop5, then run PDxPop5 and in the configuration section,
"Tools > Edit Configuration insert c:\nm74g as the NONMEM directory, and
GFORTRAN as the compiler.

General Install:
For more general installation, using your favorite compiler version, the instructions below apply
to the following compilers: Compaq/Digital Visual Fortran versions 6.6c to 6.6d, Intel Fortran
for Windows 7, 8, 9, 10, 11, and recent versions of GNU gfortran and g95. Installation on
Windows Vista or Windows 7 requires that the User Account Control be turned off. (On Vista
the path is: Control Panel -> User Accounts -> Turn User Account Control on or off. Remove the
check mark. UAC can be turned back on after installation. With Windows 7, the computer must
be restarted after turning off UAC.)

Permanently setting the system environment variable for the compiler is highly recommended for
use with PDx-Pop and so that you do not need to run a separate script or batch file every time
you want to run NONMEM. See the document on the NONMEM distribution CD-ROM,
NONMEM-PDx-Pop-Support.pdf, for information on how to set the system environment
variables via the Windows Control Panel.   The BuildEnvironmentWindowforNONMEM.pdf

provides additional information on setting up environment variables for installation with the Intel Fortran compiler on Windows.

To install NONMEM 7.4.1 follow these steps:

Read all these instruction before beginning installation.

Download the nm741CD image from a zip file:
    https://nonmem.iconplc.com/nonmem741/NONMEM7.4.1.zip

Once downloaded, unzip the file (password is obtained from IDSSOFTWARE@iconplc.com), making sure options to extract sub-directories and use of folder names are turned on.

A directory called c:\nm741CD should be produced (or wherever you decided to place the directory). Then execute the SETUP74 script to install nm741. Specific instructions for Linux, Mac or Solaris system are found in section IV.7, below.

Open a DOS terminal window. Change to the directory of nm741CD or whatever the location is you chose for the installer files:

cd nm741CD

At the command prompt, type the SETUP74 command and appropriate positional options.

SETUP74 cd h f o ar s r i u zf zu

The options are:
```
cd = source path (e.g. d:\)
h  = name of NONMEM 7.4.1 directory
f  = command for FORTRAN compiles
o  = optimization (y / n)
ar = full path name of lib/ar command
s  = same (SIZES.f90)
r  = norec (no recompile) / rec (recompile)
i  = i (interactive) / q (non-interactive)
u  = unzip program
zf = encrypted source files
zu = unencrypted files
```

The defaults are:

```
SETUP74  D:  C:\nm741  ifort  y  link  same  rec  i  unzip.exe
nonmem74e.zip nonmem74r.zip
```

The default source path d: refers to a CDROM drive, but the usual usage now is to use the unzipped contents of NONMEM 7.4.1.zip. If the gfortran compiler is used, and the installation is to proceed with user interaction, then the command is

```
SETUP74 c:\nm741CD C:\nm741 gfortran y ar same rec i
```

Note that c:\nm741CD should be replaced with the location you actually unzipped the NONMEM7.4.1.zip file.

Typical commands for other compilers, installing into [c:\nm741,](c:\nm741,) are:
Compaq Visual Fortran: `SETUP74 c:\nm741CD C:\nm741 df y link same rec i`
gfortran: `SETUP74 c:\nm741CD C:\nm741 gfortran y ar same rec i`
Intel Fortran 7 compiler: `SETUP74 c:\nm741CD C:\nm741 ifl y link same rec i`
Intel Fortran 8 and higher: `SETUP74 c:\nm741CD C:\nm741 ifort y link same rec i`

Note that with gfortran and g95, the ar command must be specified instead of link.

For installation from a CD, the source location should be the CD drive letter (such as d:) , followed by the directory name nm741CD, E.g.,
```
SETUP74 d:\nm741CD C:\nm741 ifort y link same rec i
```

For a non-interactive installation, change the final argument from i to q.
E.g.,
```
SETUP74 D:\nm741CD C:\nm741 ifort y link same rec q
```

You may ignore messages such as the following:

(a) Messages that appear at the terminal during SETUP (not new to nm74):

/Applications/Xcode.app/Contents/Developer/Toolchains/XcodeDefault.xctoolchain/usr/bin/ranli
b: file: resource.a(NM_INTERFACE.o) has no symbols
etc.

(b) Messages in finish.txt (new to nm74)

Error messages regarding klu and superlmt:
sundials/sundials_klu_impl.h:28:17: fatal error: klu.h: No such file or directory
 #include "klu.h"
etc.

A note on building the CVODES (ADVAN14) and IDAS (ADVAN15) C routines.
ADVAN14 and ADVAN15 use differential equation solvers that are descendants of ADVAN13 and ADVAN9, respectively. Most users will not need the additional versatility of these two new solvers. If you have large models, they may be of advantage. If you are using GNU gfortran, then the C routines should compile with the gcc command, which is part of the gfortran system. However, if you are using intel Fortran, and you wish to use Intel C compiler, then you will need

to purchase the Intel C compiler separately. The Intel C compiler command is icl. Alternatively, you can install the free GNU software and use its gcc compiler, which can be linked to the intel fortran compiled code.

It is not necessary to resolve the issue of C compilation at the time of installation. After installation, you can execute one of the following scripts in a terminal (command) window from the ..\pr directory:

cvode_build.bat
Execute this batch file if you used intel Fortran, and you have Intel C compiler available. Remember to set the compiler options similar to how you compiled the Fortran code of NONMEM (see your SETUP4.bat file for the compiler options you used).

cvode_buildg(64).bat
Execute this batch file (32 bit or 64 bit version) if you use gfortran for compiling the Fortran code of NONMEM.

Cvode_buildg(64)_to_ifort.bat
Execute this batch file (32 bit or 64 bit version) if you used intel Fortran, and you do not have Intel C compiler available, but you have GNU gcc/gfortran installed.

6. Test the NONMEM installation:

The SETUP74 script will run an installation test using
`nmfe74 CONTROL5 REPORT5.txt`
and will display the objective function value from the test run and the objective function from the reference file, REPORT5IDS.txt. The file "run\REPORT5.txt" will contain the complete results of the run and should be similar to "run\REPORT5IDS.txt".

The examples directory contains control streams and data files for the examples described in the "Introduction to NONMEM 7.4.1" document (see guides\nm741.pdf). Result files for these examples are also provided for reference. Note, however, that results from different compilers, and sometimes between single versus parallel computing, may vary somewhat, although they should not differ statistically significantly.

For implementation of parallelization, See Section I.55 of nm741.pdf.
New to NONMEM 7.2, and continuing with NONMEM 7.4 are sample ".pnm" files in the run directory.

IV.7 Installation on a Linux, Mac or Solaris system

The instructions below apply to the following system configurations: Linux or Mac or Solaris, with Intel 9,10,11, or recent versions of g95 or GNU gfortran.

Permanently setting the system environment variable for the compiler is highly recommended for use with PDx-Pop and so that you do not need to run a separate script or batch file every time you want to run NONMEM.

Downloading the NONMEM7.4.1 CD Image from ICON's NONMEM ftp site**:**

Open a Safari or Google Chrome or other browser window. Type into the search bar:

https://nonmem.iconplc.com/nonmem741

or other suitable sub-directory

Click on the file NONMEM7.4.1.zip
This should start the download.

When it is finished, open a terminal window for the remainder of the install.

(Note: Do not try to unzip the file NONMEM7.4.1.zip in Finder. This will attempt to use the Apple Archive utility, which will fail with an error message.)

To open a terminal window, open a Finder window, click on Applications, click on Utilities, click on Terminal.app. Any shell (e.g, bash or csh) may be used.

In the terminal window, type

```
cd Downloads
unzip NONMEM7.4.1.zip
            (password is  obtained from IDSSOFTWARE@iconplc.com)
cd nm741CD
```

Now proceed to instruction 5 below for the SETUP74 command with the following options:

- Option cd (source path) should be $HOME/Downloads/nm741CD
- Option h (NONMEM 7.4 directory) is up to you. $HOME/nm741 is suggested.

If gfortran is installed, the command would be as follows:

```
/bin/bash SETUP74 $HOME/Downloads/nm741CD $HOME/nm741 gfortran
```

NONMEM 7.4 will be installed in directory nm741, in the user's home directory.
Any new terminal window that is opened will be in the user's home directory.

To install NONMEM 7.4.1 from a CD, follow these steps:

1. Read all these instruction before beginning installation.

2. Open a Terminal window. Any shell (e.g, bash or csh) may be used.

3. Place the NONMEM_7.4.1 CD in the CD drive.
The path for the CD will differ from one OS to another. Possible locations for auto mounting include:
Solaris 10: /cdrom/cdrom0
Redhat: /mnt/cdrom
ubuntu: /media/cdrom
Other Linux: /cdrom
Mac OS X: /Volumes/NONMEM_7.4.1

4. Change to the CD, e.g., "`cd /mnt/cdrom`"

5. Type /bin/bash SETUP74 command and appropriate positional options.

```
/bin/bash SETUP74 cd h f o ar s r i u zf zu

The options are:
          cd = source path (e.g. /mnt/cdrom).
           h = name of NONMEM 7.4 directory
           f = command for FORTRAN compiles
           o = optimization (y | n)
          ar = full path name of ar command
           s = same (SIZES.f90)
           r = norec (no recompile) | rec (recompile)
           i = i (interactive) | q (non-interactive)
           u = unzip program
           zf = encrypted source files
           zu = unencrypted files

Default:

SETUP74 /mnt/cdrom /Users/Shared/nm741 ifort y /usr/bin/ar same
rec i unzip nonmem74e.zip nonmem74r.zip
```

If the gfortran compiler is used and NONMEM 7.4.1 is to be installed from the CD located at /mnt/cdrom0 into the /Users/Shared/nm741 directory with optimization, the default ar command is to be used, and the installation is to proceed with user interaction, then the command is:

```
 /bin/bash SETUP74 /mnt/cdrom0 /Users/Shared/nm741 gfortran y ar
same  rec i
```

Typical commands for other compilers, installing into /Users/Shared/nm741 are:

gfortran:
```
/bin/bash SETUP74 /mnt/cdrom0 /Users/Shared/nm741 gfortran y ar
same rec i
```
Intel Fortran 8-11:
```
/bin/bash SETUP74 /mnt/cdrom0 /Users/Shared/nm741 ifort y ar
same rec i
```

For installation from a directory, copy the files from the CD to the directory from which the installation will be performed, or unzip the NONMEM7.4.1.zip file into the directory from which installation will be performed. The path to this directory is the first argument for the /bin/bash SETUP74 command.

E.g.,
```
/bin/bash SETUP74 /Users/Shared/Downloads/nm741CD
 /Users/Shared/nm741 ifort y ar same rec i
```

For Solaris with f95, include the path to ar and unzip, e.g.,
```
/bin/bash SETUP74 /Users/Shared/Downloads/nm741CD
 /Users/Shared/nm741 f95 y /usr/ccs/bin/ar same rec i
 unzip
```

The installation may fail on Solaris 10 with the message

./util/dotest: line 74: gcc: command not found
Could not assemble util/test.c with gcc
Compiler f95 and/or install program cannot be run

If so, copy the CD to your own directory. Edit SETUP74 and change
./util/dotest $f
to
./util/dotest $f
Now do the installation from your own directory.

For a non-interactive installation, change the final argument from i to q.
E.g.,
```
/bin/bash SETUP74 /Users/Shared/Downloads/nm741CD
 /Users/Shared/nm741 f95 y /usr/ccs/bin/ar same rec q
```

You may ignore messages such as the following:

(a) Messages that appear at the terminal during SETUP (not new to nm74):

/Applications/Xcode.app/Contents/Developer/Toolchains/XcodeDefault.xctoolchain/usr/bin/ranli
b: file: resource.a(NM_INTERFACE.o) has no symbols
etc.

(b) Messages in finish.txt (new to nm74)

In file included from cvodes_klu.c:28:0:
sundials/sundials_klu_impl.h:28:17: fatal error: klu.h: No such file or directory
 #include "klu.h"
etc.

A note on building the CVODES (ADVAN14) and IDAS (ADVAN15) C routines.
ADVAN14 and ADVAN15 use differential equation solvers that are descendants of ADVAN13
and ADVAN9, respectively. Most users will not need the additional versatility of these two new
solvers. If you have large models, they may be of advantage. If you are using GNU gfortran,
then the C routines should compile with the gcc command, which is part of the gfortran system.
However, if you are using intel Fortran, and you wish to use Intel C compiler, then you will need
to purchase the Intel C compiler separately. The Intel C compiler command is icl. Alternatively,
you can install the free GNU software and use its gcc compiler, which can be linked to the intel
fortran compiled code.

It is not necessary to resolve the issue of C compilation at the time of installation.   After
installation, you can execute one of the following scripts in a terminal (command) window from
the ..\pr directory:

cvode_build.bsh
Execute this script file if you used intel Fortran, and you have Intel C compiler available.
Remember to set the compiler options similar to how you compiled the Fortran code of
NONMEM (see your SETUP4.bat file for the compiler options you used).

cvode_buildg.bsh
Execute this batch file if you use gfortran for compiling the Fortran code of NONMEM. You
may also execute this script file if you used intel Fortran, and you do not have Intel C compiler
available, but you have GNU gcc/gfortran installed.

6. Test the NONMEM installation:

The SETUP74 script will run an installation test using
`nmfe74 CONTROL5 REPORT5.txt`
and will display the objective function value from the test run and the objective function from the
reference file, REPORT5IDS.txt.   The file "run/REPORT5.txt" will contain the complete results
of the run and should be similar to "run/REPORT5IDS.txt".

The examples directory contains control streams and data files for the examples described in the
"Introduction to NONMEM 7.4.1" document (see guides/nm741.pdf).   Result files for these

examples are also provided for reference. The user may want to run these examples as well for a more extensive qualification of the installation.

For implementation of parallelization, See Section I.55 of nm741.pdf.
New to NONMEM 7.2 are sample ".pnm" files in the run directory.

IV.8 Compiler test for Windows systems

Due to the fact that most installation problems are caused by incomplete compiler or linker installation, prior to installing NONMEM a test of your compiler is appropriate to assure that your compiler is properly configured. An example of Fortran source code follows. Create a file named hello.for using Notepad.exe containing the following text:

```
C234567
      program test
      WRITE (6,*) "Hello, NONMEM World!"
      end
```

(The first line begins with column 1 ([this is a comment line that acts as a column number guide], lines 2,3, & 4 begin in column 7.)

Save the file and compile it from a DOS command line using the compiler command for your compiler.
For Intel 8, 9, 10, 11, "ifort hello.for"
For g95, "g95 hello.for -o hello.exe"
For gfortran, "gfortran hello.for -o hello.exe"
For Digital/Compaq, "df hello.for"

Run the compiled program at the command line, by typing hello followed by the Enter key. If successful, the output will be as expected:

```
C:\>ifort hello.for -o hello.exe

C:\>hello
 Hello, NONMEM World!

C:\>
```

If not successful, you will get an error either indicating that the compiler was not found:

'ifort' is not recognized as an internal or external command, operable program or batch file.

or a compiler error of some other type.

The most probable cause of these errors is that the environment variables for the compiler and/or the linker (Microsoft Visual Studio provides the linker for Digital/Compaq and Intel Fortran) are not set so that these programs may be run from a DOS window. This requires that the environment variables are set for the system which is usually done using the Control Panel if the installation for the compiler or MS Visual Studio has not set them. The compiler test must be successful before you can install NONMEM. Please note that this simple compiler test may not detect problems with the linking process.

IV.9 Additional Mac OS X issues

IV.9.1 Missing Unix commands

Mac OS X may not include certain Unix commands that are needed for NONMEM installation: ar as ranlib ld gcc make

It is possible that they have been previously installed. In a terminal window type the command
gcc
If the response is
i686-apple-darwin10-gcc-4.2.1: no input files
(or fatal error: no input files, or something similar) then the commands have been installed. Proceed as directed above for Mac OS X installation.
If the response is "gcc: Command not found" or an alert box is opened as below, then these commands must be installed before NONMEM can be installed. There are several ways this can be done.

With macOS Sierra Version 11.12 (and some earlier versions starting with Mavericks 10.9), the response to gcc may be an alert box containing this text:

The "gcc" command requires the command line developer tools.
Would you like to install the tools now?
Choose Install to continue. Choose Get Xcode to install Xcode and the command line developer tools from the App Store.

Click on the blue **Install** button. This will install the necessary commands from the App Store without the full Xcode package. You must be connected to the internet.

With other earlier versions of Mac OSX, it may be necessary to install the version of Xcode that corresponds to the OS X version.
These can be found by browsing https://developer.apple.com/download/more/
You may have to create a developer login, but this should be free with your Apple ID.

It may be easier to upgrade to Sierra than to download Xcode.
Upgrades to Sierra from OS X Yosemite 10.10 and OS X El Capitan 10.11 have been performed

---

easily. We have no experience with upgrades to Sierra from older versions of OS X.

Be sure to backup your system before attempting any upgrade.

Installation of gcc may require some time (more than 20 minutes for some setups), so be patient.

The following information was written for earlier versions of NONMEM and MacOS.

You may install them from the Mac OS X Install Disks.

For example, with Mac OS X version 10.5 (Leopard), Xcode Tools is on Install Disc 2.
Click on "Xcode Tools" and then "Xcode Tools.mpkg"
Only the UNIX Development Tools need be installed.

If you do not have the Install Disks, you may register with Apple as a developer at
http://developer.apple.com/technologies/tools/xcode.html
and get the Xcode Free Download package for your version of Mac OS X.

For Mac OS X 10.6 (Snow Leopard), click on "Xcode 3 Free Download " and "Mac Dev Center".
Only the UNIX Development Tools need be installed.

There is a discussion of these two options at http://www.webmo.net/support/fortran_osx.html
See SOFTWARE DEVELOPMENT UTILITIES AND C COMPILER

When gcc and the other commands have been installed, proceed as directed above for Mac OS X
installation.

IV.9.2 Choosing 32-bit vs. 64-bit binaries

The compiler and gcc must produce the same kind of binaries by default.
The util directory contains two files: test.c test.f90
Check that they produce the same kind of binaries, e.g.,

On Mac OS X 10.6 (Snow Leopard)
% gfortran test.f90; file a.out
a.out: Mach-O 64-bit executable x86_64
% gcc test.c ; file a.out
a.out: Mach-O 64-bit executable x86_64

On Mac OS X 10.5 (Leopard)
% gfortran test.f90; file a.out
a.out: Mach-O executable i386
% gcc test.c ; file a.out

a.out: Mach-O executable i386

SETUP74 will work correctly with gfortran when the a.out's are consistent.
If you have a compiler other than gfortran and the a.out's are inconsistent, contact us and we will work with you on this.

IV.9.3 Mounting file systems for MPI

It is easier to use afp (Apple Filing Protocol) than nfs .

To export a file system or folder to another Mac:
 Select the Apple menu / System Preferences / Sharing / File Sharing
Under "shared folders:" click + and select the folder e.g., mydir
Under "users:" click + and select the users.

To mount a file system or folder from another Mac:
Open a finder window.
You should see the hostname of the other computer listed under "Shared"
Click on it. Click on "connect as"
Enter the username and password.
Click on the folder, e.g., mydir
The file system or folder will be mounted as /Volumes/mydir

E.g., in a terminal window: % ls /Volumes/mydir

IV.9.4 Enabling ssh with no password for OS X

Select the Apple menu / System Preferences / Sharing / Remote Login
The instructions for Linux (using ssh-keygen) should work on Mac OS X.
There may be an interaction with keychain, and this may be problematic.

If "ssh –n" cannot be made to work, you can use the workaround for mpdboot described in the MPICH2 Installer's Guide.
See 'start the daemons "by hand"' on page 7 of mpich2-1.2.1-installguide.pdf

IV.9.5 Installing MPICH2

MPICH2 must be compiled and installed for Mac OS X.
Please look at mpich2/README_vin.mht and the other documents.

First, see what kind of binaries have been installed, e.g.,
% cd /Users/Shared/nm741/mpi/mpi_ling (or mpi_lini, with ifort):
% file mpi.o

You will see either of the following:
mpi.o: Mach-O 64-bit object x86_64
mpi.o: Mach-O object i386
"i386" indicates 32 bit binaries.

Suggested options for the configure step:

If SETUP74 installed 64 bit binaries:
./configure --prefix=/usr/local/mpi64 CFLAGS="-m64" FFLAGS="-m64" --enable-f90 --disable-cxx | & tee c.txt

If SETUP74 installed 32 bit binaries:
./configure --prefix=/usr/local/mpi32 --enable-f90 | & tee c.txt

Either way, continues with
make |& tee m.txt
make install |& tee mi.txt

Then replace libmpich.a, in the NONMEM 74 directory, e.g, if 64 bit was installed:
cd /Users/Shared/nm741/mpi/mpi_ling
cp libmpich.a libmpich.a.orig
cp /usr/local/mpi64/lib/libmpich.a libmpich.a

IV.9.6 Using the Correct MPI commands

The user's path should be set so that commands such as mpirun and mpf90 from MPICH2 are used instead of the corresponding Open MPI commands native to Mac OS X.
For example, if 64 bit was installed, the following is suggested prior to doing one or more NONMEM runs with MPI in a csh window:

   % set path = (/usr/local/mpi64/bin $path)

If this is not done, the message may appear:
   Unfortunately, this installation of Open MPI was not compiled with
   Fortran 90 support. As such, the mpif90 compiler is non-functional.

IV.10 Setting up NONMEM's environment Variable System

A feature of the execution script file nmfe74 is that the path to the fortran compiler system and MPI system that is appropriate for NONMEM may be specified in a script file that could have the following environment variables defined:

compilerpath
mpibinpath
mpilibpath
mpilibname

Comments in these files are provided for instructions about each of these environment variables. These paths will be temporarily added to the front of the PATH environment variable, so that the appropriate compiler or MPI system is called to service NONMEM. In the past, conflicts with other installed fortran compilers from other applications would prevent the appropriate compiler from being used for the NONMEM system. This location file method allows NONMEM to be forced to look in a particular location.

The location file should be called nmloc.bat or nmloc by convention. It may be specified at the nmfe74 command line by the -locfile option, for example:

nmfe74 myfile.ctl myfile.res -locfile=nmloc.bat

If –locfile is not specified, the nmfe74 script looks in the present working directory for nmloc.bat (windows) or nmloc (linux). If this file is not found, it looks in the top directory of the NONMEM installed directory. Thus, the file nmloc.bat (Windows) or nmloc (Linux) in the top nonmem installed directory serves as the default location file, and may be modified, or used as a template and placed in the working directory or specified in the –locfile option on the command line. If a particular environment variable in the above list is not found or is not defined, then nmfe74 will behave as in earlier versions, and rely on the presently existing PATH for finding the compiler and MPI system. The nmfe74 script will display a statement as to what path it will use.

To find environment variables for your fortran compiler, you can use the "which" command in Linux based operating systems. Open a terminal window and type the command

which gfortran
or
which ifort
depending on your compiler.

As an example, this may return
/usr/local/bin/gfortran

Next, locate the file nmloc in the top directory of your NONMEM installation. The environment variable "compilerpath" needs to be modified to point to this directory, for example:
compilerpath=/usr/local/bin:/usr/bin

You can do the same for finding the path to your MPI system:

which mpiexec

or whatever the executable name of your MPI system is, and populate the environment variable "mpibinpath" in the nmloc file.