

Practice Guidelines

Why and if so how?

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Case

- A 65 year old woman with low risk MDS, subtype RARS is referred to you
- She is red cell transfusion dependent 2 units every month and has received a cumulative of 30 units
- Her projected life expectancy exceeds 5 years
- Her ferritin is 1500
- What should you recommend?



Why Do We Need Practice Guidelines?



Keeping Up-to-Date

- **medical literature doubles every 10 years**
- **there are 23,000 biomedical journals**
- **2,000,000 articles are published per year**
- **reading the top 10 medical journals requires:**
 - **reading 200 articles per month**
 - **reading 70 editorials per month**

- Substantial pressure to change practice on basis of weak data
 - Media
 - Patient pressure
 - Pharmaceutical industry



- Geographic and other barriers to information

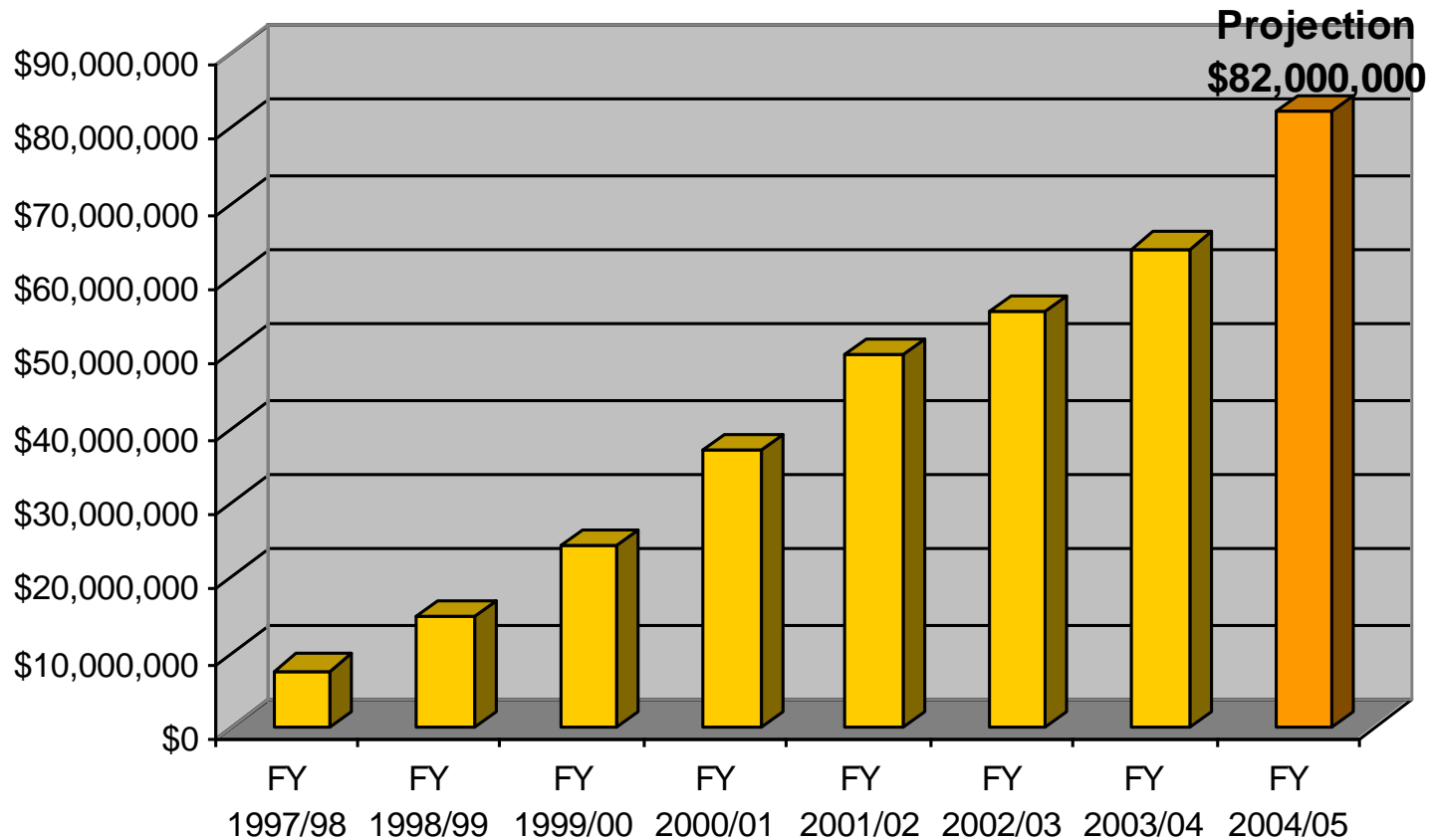


Resource Implications

- Not the primary driver for guidelines
- Assist in planning and limiting unexplained variability in resource use
- Can help inform funding decisions
- The Ontario experience:
 - Has helped encourage uptake of new agents more than limit their use



NDFP Annual Expenditures

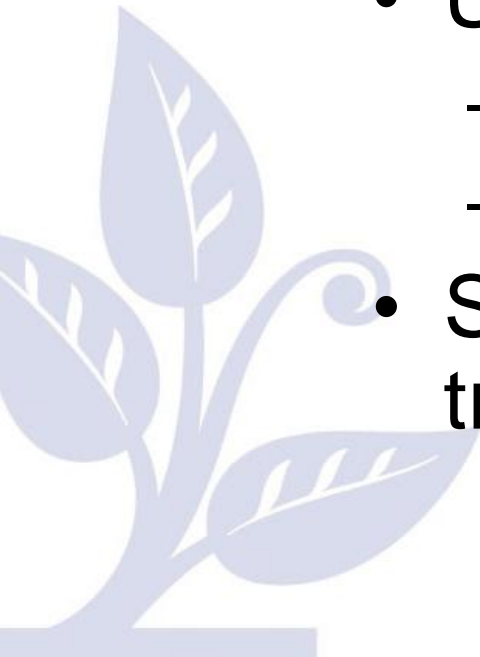


Types of Evidence



Phase I Trial

- Objective:
 - Determination of optimal dose
- Uses:
 - Helps guide further studies
 - Provides biological insight
- Should not be used to guide treatment policies



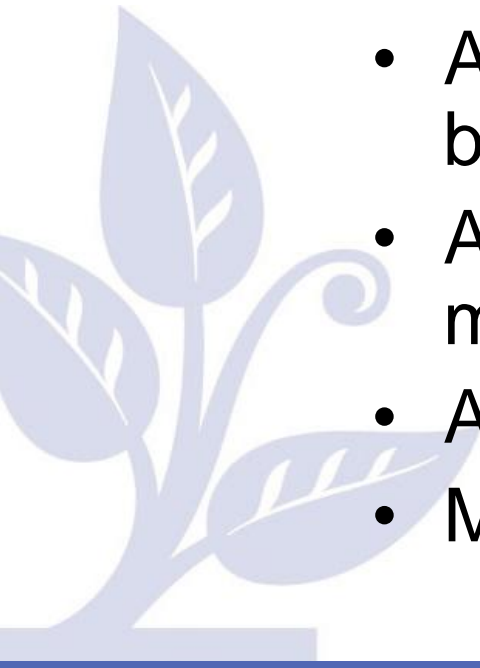
Phase II Trials

- Goal:
 - Estimate efficacy and toxicity
- Uses:
 - Assist in development of randomized trials
- Use of phase II trials to guide policy hazardous
 - Phase II results consistently overestimate benefit
 - Effect highly dependant on eligibility criteria
 - Comparison across Phase II trials particularly dangerous



Steered the Wrong Way by Phase II Trials

- Superiority of 2nd/3rd generations over CHOP in lymphoma
- Hybrid regimens in Hodgkin's
- Autologous stem cell transplantation for breast cancer
- Aggressive multi-agent chemotherapy in myeloma
- Anagrelide in Essential thrombocytosis
- Many others



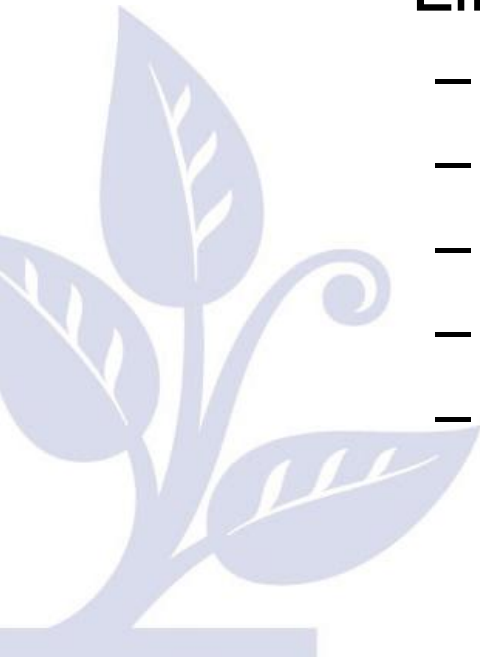
Phase III Trials

- Goal:
 - Comparisons to standard treatment
- Uses:
 - Influence treatment policies
- Cautions when interpreting single RCT's
 - Difficult to generalize to other populations
 - Effect not always consistent in same population
 - Not all RCTs rigorously conducted
 - Rare instances of fraud (eg. Bezwoda)



Meta-Analysis

- Definition:
 - Statistical combination of results of several studies to generate single effect estimate
- Limitations:
 - “garbage in, garbage out”
 - Selection bias
 - Publication bias
 - Imprecision
 - “combination urge”



Outcomes



Outcomes that should regularly influence policy

- Survival
- Quality of life
- Economic benefit



Outcomes that should sometimes influence policy

- Progression-free survival
 - When magnitude substantial
 - Where good reason to think progression predicts survival or influences quality of life
- Toxicity
- ?Hospitalization



Hierarchy of Trials:

Meta-analyses

Randomized Trials

Cohort Comparisons

Case Series

Case Reports

Ways to Synthesize the Evidence



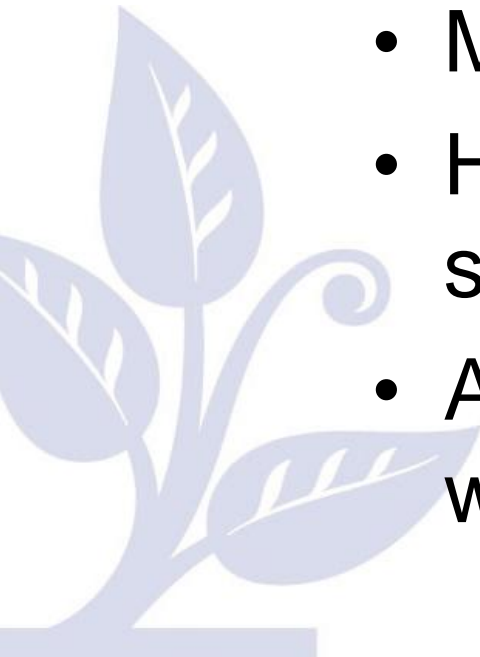
Book Chapters

- Not an effective resource for up-to-date treatment advice
- Limitations:
 - Long publication lag (less with E-resources)
 - Single author
 - Generally no published methodology
 - Unclear target audience



Review Article

- Published overview of a topic
- No standard format
- May or may not be evidence-based
- Highly dependant on the “expert” status of the author
- Authors often highly selective of what information to include



Systematic Review

- Structured review of literature:
 - Explicit description of databases searched
 - Abstracts, non-English language, unpublished data
 - Clearly identified search strategy
 - Clear inclusion and exclusion criteria
 - Identification of how data will be pooled



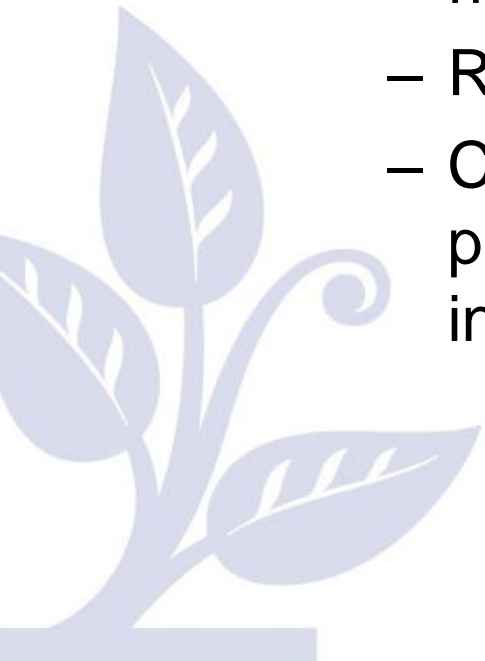
Systematic Review

- **Advantages**

- Methodologically rigorous
- Reproducible
- Common framework for presenting and interpreting data

- **Disadvantages**

- Very time and resource intensive
- Best suited to questions for which there is high quality data
- Interpretation often needed



Practice Guideline

- A document meant to assist practitioners in treating patients
- Often evidence-based (not always)
- Authors:
 - Local institutional policies
 - Expert consensus opinion of professional bodies
 - Government agencies
 - Journals or other publications
 - Cochrane collaboration



Not all Guidelines Created Equal



Practice guidelines

- Should include a systematic review
- Should clearly distinguish evidence from opinion
- The data rarely good enough without some form of interpretation:
 - Weighing outcomes
 - Generalization to other populations
 - Placing in context with other therapies
 - Reflecting local funding and other realities
- Ideally should provide principles for decision making



What to look for in a guideline

- A systematic review component
- A respected sponsoring agency
- A review process (ideally external)
- Practical guidance for practice
- A practice context comparable to your own

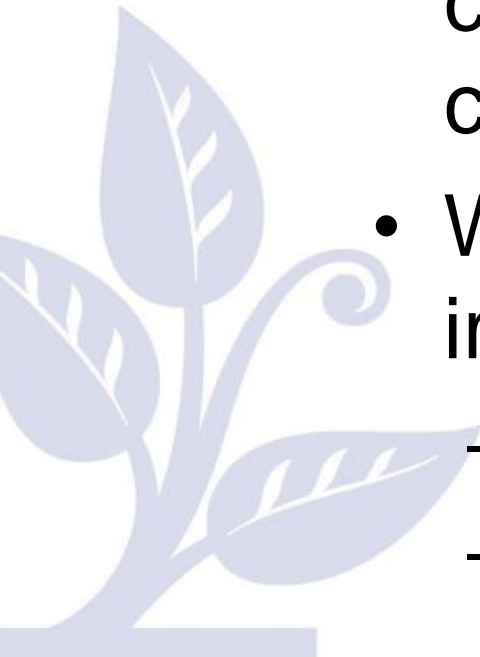


Back to our patient



Iron chelation guidelines

- December 2005: 11 Canadian hematologists experts in MDS convened to answer the following critical questions:
- Why, whom, when and how to treat iron overload in patients with MDS?
 - 4 groups
 - submitted for publication Dec 2007





Available online at www.sciencedirect.com



Leukemia Research 32 (2008) 1338–1353

**Leukemia
Research**

www.elsevier.com/locate/leukres

Invited editorial

Iron overload in myelodysplastic syndromes: A Canadian consensus guideline

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Canadian Guidelines 2007

- **Why:** to prevent end-organ complications of iron overload and extend lifespan
 - **Whom:** transfusion-dependent patients with expected survival > 1 year **or** BMT candidates
 - **When:** ferritin >1000, TfSat > 0.5
 - **How:** DSX 20 mg/kg/d or DFO 50 mg/kg/d 5/7; target ferritin <1000
- 

Management of IOL

Guidelines for ICT in MDS

- Italian Society of Hematology (2002)
- United Kingdom MDS guidelines (2003)
- Nagasaki Consensus Statement (2005)
- National Comprehensive Care Network (2007)
- [Canadian Consensus Guidelines \(2008\)](#)
- Japanese guidelines (2008)
- Consensus statement (2008)
- Austrian guidelines (2008)
- Israeli Guidelines (2008)
- MDS Foundation International Guidelines (in dev)
- European LeukemiaNet Guidelines (in dev)



Conclusions

- Practice guidelines a convenient resource to help ensure optimal patient care
- Learn to trust specific sponsoring agencies as not all guidelines are created equal
- Many resources just one Google away





Sunnybrook

- MDS Center of excellence May 2006
 - Established university program
 - Morphologic expertise in MDS
 - Available cytogenetics and molecular genetics
 - Research including REB approved studies
 - Peer reviewed publications in the field
 - Ability and intention to register patients in an international MDS registry

MDS Program at Sunnybrook

- 4 years old
- >300 patients registered in database
- 120 with QOL completed at least once
- Computerized soon to be web-based
- National grant proposal to CIHR



FACT-An

MDS database

Patient initials: _____ F. M. L.	Study #: _____
Clinic file #: _____	Hospital file #: _____
Investigator: _____	This box to be completed by staff

FACT-An (version 4)

Visit # _____ **Date of assessment:** ____-____-____
dd-mm-yyyy

Below is a list of statements that other people with your illness have said is important. By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

PHYSICAL WELL-BEING		Hot at all	A little bit	Some what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

SOCIAL/FAMILY WELL-BEING		Hot at all	A little bit	Some what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	<i>Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please check this box <input type="checkbox"/> and go to the next section</i>					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-An

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

EMOTIONAL WELL-BEING		Hot at all	A little bit	Some what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping my illness	0	1	2	3	4
GE3	I am losing hope in the fight with my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

⊕

FUNCTIONAL WELL-BEING		Hot at all	A little bit	Some what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

⊕

ADDITIONAL CONCERNS		Hot at all	A little bit	Some what	Quite a bit	Very much
HI7	* I feel fatigued	0	1	2	3	4
HI12	* I feel weak all over	0	1	2	3	4
An1	* I feel listless ("washed out")	0	1	2	3	4
An2	* I feel tired	0	1	2	3	4
An3	* I have trouble <u>starting</u> things because I am tired	0	1	2	3	4
An4	* I have trouble <u>finishing</u> things because I am tired	0	1	2	3	4
An5	* I have energy	0	1	2	3	4
An6	I have trouble walking	0	1	2	3	4
An7	* I am able to do my usual activities	0	1	2	3	4
An8	* I need to sleep during the day	0	1	2	3	4
An9	I feel lightheaded (dizzy)	0	1	2	3	4
An10	I get headaches	0	1	2	3	4
B1	I have been short of breath	0	1	2	3	4
An11	I have pain in my chest	0	1	2	3	4
An12	* I am too tired to eat	0	1	2	3	4
BL4	I am interested in sex	0	1	2	3	4
An13	I am motivated to do my usual activities	0	1	2	3	4
An14	* I need help doing my usual activities	0	1	2	3	4
An15	* I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	* I have to limit my social activity because I am tired	0	1	2	3	4

* These items comprise the 13-item fatigue scale

Patient's Signature: _____

Date: _____
dd-mo-yyy

CRA Signature: _____

Date: _____
dd-mo-yyy

EORTC QLQ-C30

MDS database

Patient initials: _____ F. M. L.	Study #: _____
Clinic file #: _____	Hospital file #: _____
Investigator: _____	<small>This box to be completed by staff</small>

EORTC QLQ-C30 (version 3)

Visit #: _____ **Date of assessment:** ____-____-____
dd-mon-xxxx

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

		Hot at all	A little	Quite a bit	Very much
1	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2	Do you have any trouble taking a long walk?	1	2	3	4
3	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4	Do you need to stay in bed or a chair during the day?	1	2	3	4
5	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

6	Were you limited in doing either your work or other daily activities?	1	2	3	4
7	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8	Were you short of breath?	1	2	3	4
9	Have you had pain?	1	2	3	4
10	Did you need to rest?	1	2	3	4
11	Have you had trouble sleeping?	1	2	3	4
12	Have you felt weak?	1	2	3	4
13	Have you lacked appetite?	1	2	3	4
14	Have you felt nauseated?	1	2	3	4
15	Have you vomited?	1	2	3	4

During the past week:

		Hot at all	A little	Quite a bit	Very much
16	Have you been constipated?	1	2	3	4
17	Have you had diarrhea?	1	2	3	4
18	Were you tired?	1	2	3	4
19	Did pain interfere with your daily activities?	1	2	3	4
20	Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21	Did you feel tense?	1	2	3	4
22	Did you worry?	1	2	3	4
23	Did you feel irritable?	1	2	3	4
24	Did you feel depressed?	1	2	3	4
25	Have you had difficulty remembering things?	1	2	3	4
26	Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27	Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28	Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29 How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30 How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Patient's Signature: _____ Date: ____-____-____
dd-mon-xxxx

CRA Signature: _____ Date: ____-____-____
dd-mon-xxxx

Jul 12, 2007 EORTC QLQ-C30

Global Fatigue

MDS database	
Patient initials: _____ <small>F, M, L</small>	Study #: _____
Clinic file #: _____	Hospital file #: _____
Investigator: _____	<small>This box to be completed by staff</small>

Global Fatigue Question

Visit # _____ Date of assessment: _____
dd-mmm-yyyy

On the scale below please **circle** the number that best describes your **overall level of fatigue during the past week**.

0 1 2 3 4 5 6 7 8 9 10

No Fatigue Worst Possible Fatigue

Patient's Signature: _____ Date: _____
dd-mmm-yyyy

CRA Signature: _____ Date: _____
dd-mmm-yyyy

Jul 12, 2007 Global Fatigue Question

EQ-5D

MDS database

Patient initials: _____ <small>F, M, L</small>	Study #: _____
Clinic file #: _____	Hospital file #: _____
Investigator: _____	

This box to be completed by staff

EQ-5D Questionnaire

Visit # _____ **Date of assessment:** ____-____-____
dd-mon-yyyy

By placing a tick in one box in each group below, please indicate which Statements best describe your own health state today.

Mobility

I have no problems in walking about	<input type="checkbox"/> 1
I have some problems in walking about	<input type="checkbox"/> 2
I am confined to bed	<input type="checkbox"/> 3

Self Care

I have no problems with self-care	<input type="checkbox"/> 1
I have some problems washing or dressing myself	<input type="checkbox"/> 2
I am unable to wash or dress myself	<input type="checkbox"/> 3

Usual Activities (e.g. work, study, housework, family or leisure activities)

I have no problems with performing my usual activities	<input type="checkbox"/> 1
I have some problems with performing my usual activities	<input type="checkbox"/> 2
I am unable to perform my usual activities	<input type="checkbox"/> 3

Pain/Discomfort

I have no pain or discomfort	<input type="checkbox"/> 1
I have moderate pain or discomfort	<input type="checkbox"/> 2
I have extreme pain or discomfort	<input type="checkbox"/> 3

Anxiety/Depression

I am not anxious or depressed	<input type="checkbox"/> 1
I am moderately anxious or depressed	<input type="checkbox"/> 2
I am extremely anxious or depressed	<input type="checkbox"/> 3

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

**Your own
health state
today**

Patient's Signature: _____ Date: ____-____-____
dd-mon-yyyy

CRA Signature: _____ Date: ____-____-____
dd-mon-yyyy

Jul 12, 2007 EQ-5D Questionnaire

QOL Instrument	Factor	P value
FACT-An		
Anemia subscale	Transfusion	.01
Trial Outcome index	Transfusion	.01
Fatigue Subscale	Transfusion	.04
EORTC		
Physical function	Age	.003
	Transfusion	.004
Social Function	Transfusion	.002
Global Health Status	Hgb	.02
Fatigue	Hgb	.009
Dyspnea	Hgb	.03
Appetite Loss	Age	.004
Financial Problems	Transfusion	.001
Global Fatigue, EQ-5D	Transfusion	.02 & .04

Other guidelines in development nationally

- Guidelines for MDS management
 - Growth factors
 - Hypomethylating agents
 - Histone deacetylase inhibitors
 - Stem cell transplant
 - Immunomodulatory drugs
 - Immunosuppressive therapy
 - Low dose chemotherapy
 - Conventional dose chemotherapy
 - MDS/MPD
 - Pediatric MDS
 - Supportive care and transfusion therapy

